

Implementing Virtual Strategies Across an Integrated Healthcare System: IMPLEMENT-HF

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Virtual**



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Disclosures

- ASB has previously received consulting fees from Sanofi Pasteur, Verve Therapeutics, and Novocardia Health.

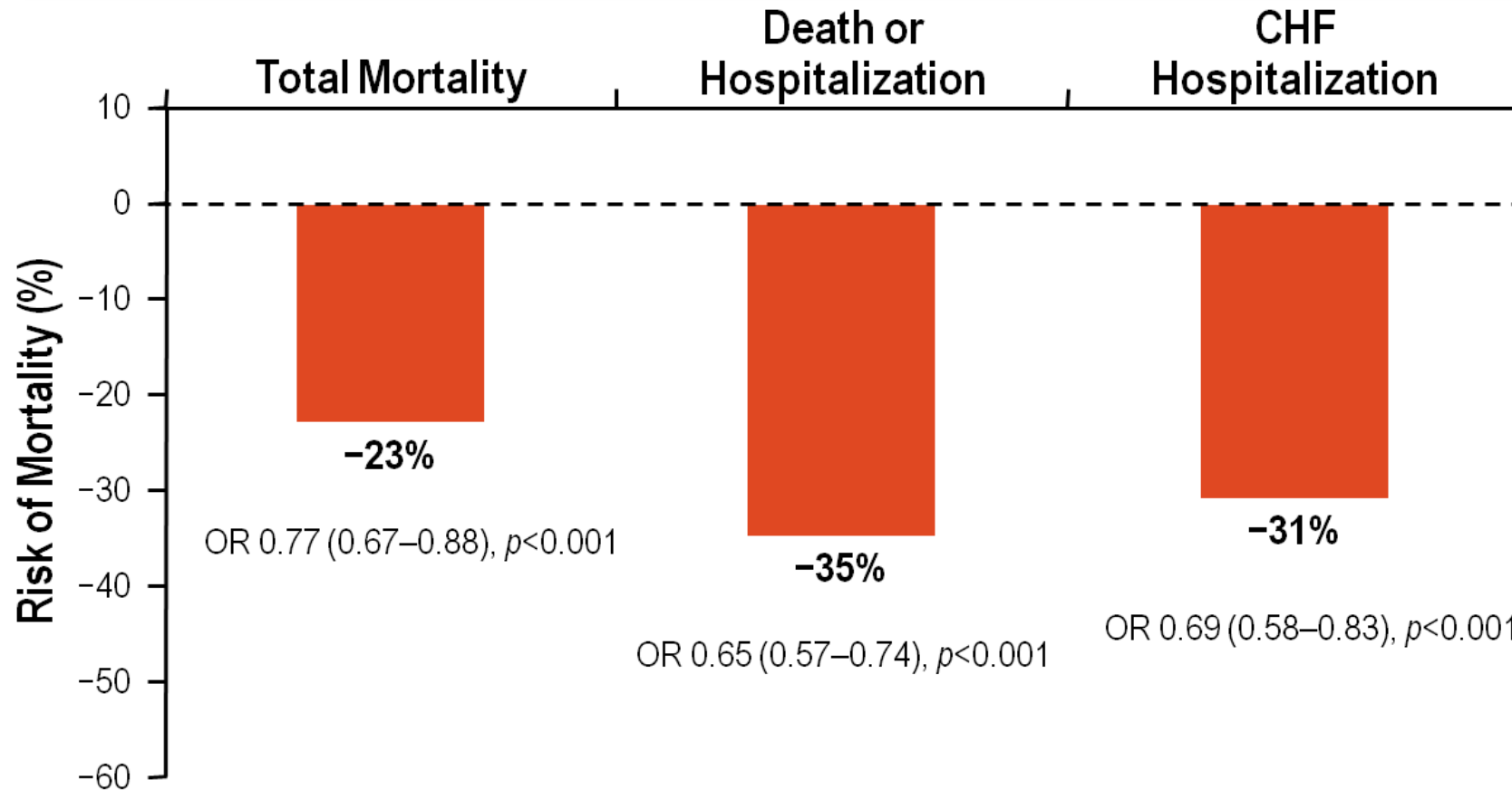
Nomenclature



Classification	Ejection Fraction
Heart Failure with Reduced Ejection Fraction (HFrEF)	$\leq 40\%$
Heart Failure with Mildly Reduced Ejection Fraction (HFmrEF)	41% to 49%
Heart Failure with Preserved Ejection Fraction (HFpEF)	$\geq 50\%$
Heart Failure with Improved Ejection Fraction	$\leq 40\% \rightarrow > 40\%$ with a 10% increase

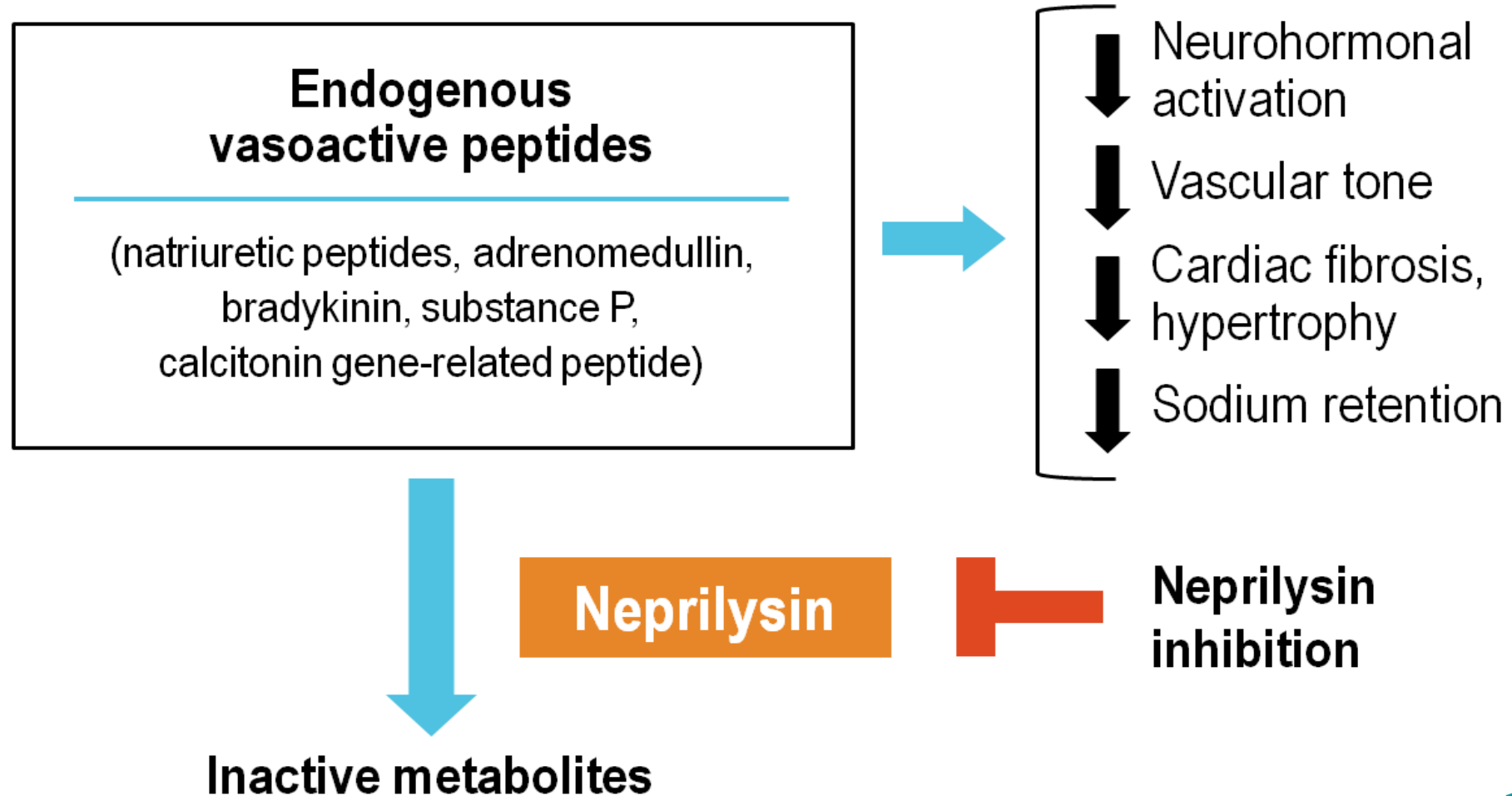
ACEi Lower Mortality and Hospitalizations in HFrEF

32 Trials of ACEI in Heart Failure: ACEI (n=3870) vs. Placebo (n=3235)



OR = odds ratio

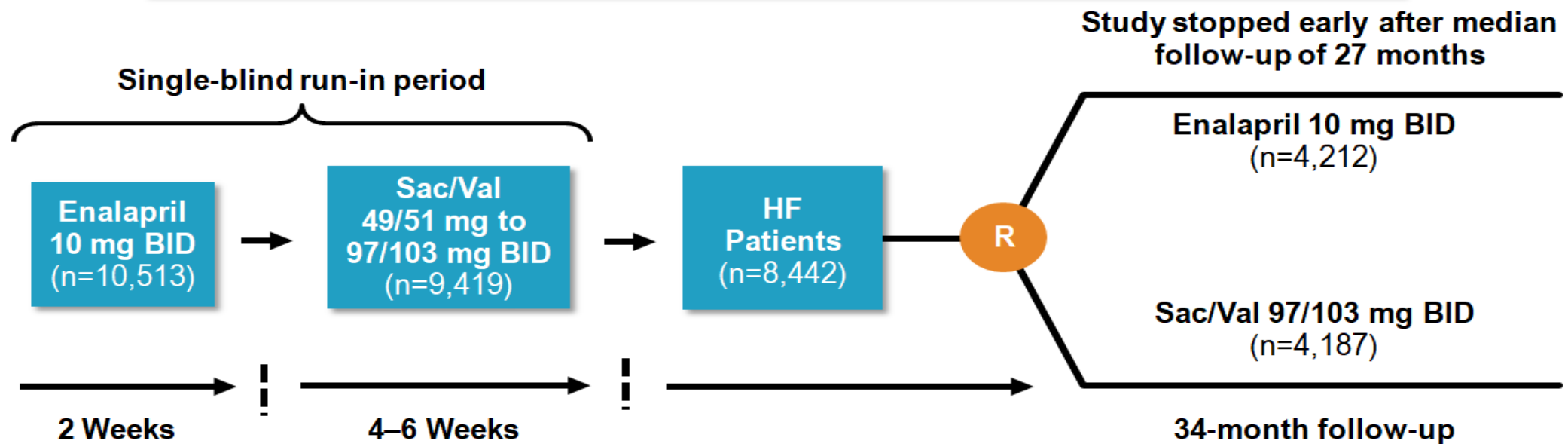
Effects of Neprilysin Inhibition in HF



PARADIGM-HF: Trial Design

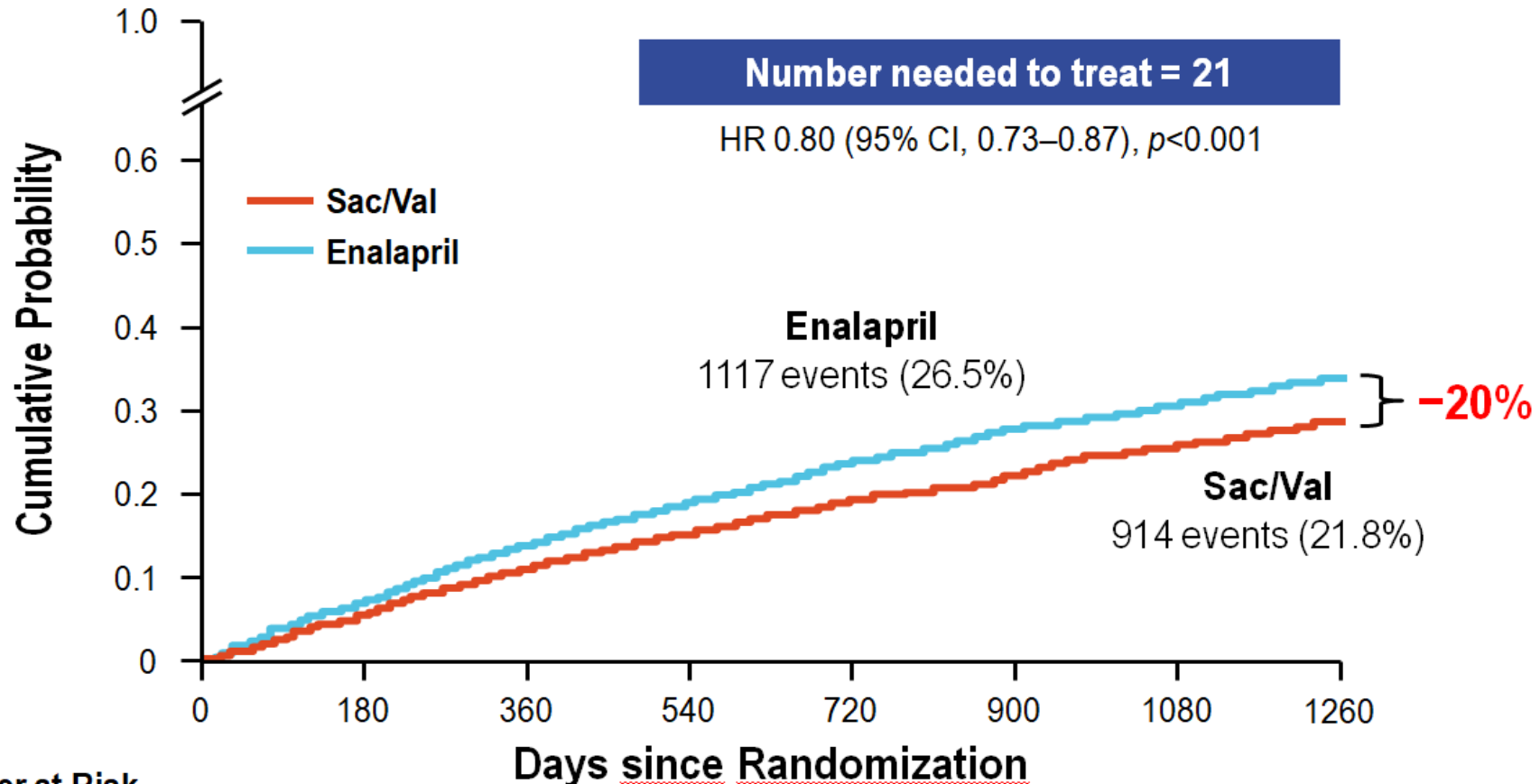
Entry Criteria:

- NYHA class II-IV HF, LVEF $\leq 40\%$ → amended to $\leq 35\%$
- BNP ≥ 150 pg/mL (or NT-proBNP ≥ 600 pg/mL) or 1/3 lower if hospitalized for HF within 12 months
- On a stable dose of ACEI or ARB equivalent to ≥ 10 mg of enalapril daily for ≥ 4 weeks
- Unless contraindicated, on stable dose of beta-blocker for ≥ 4 weeks
- SBP ≥ 95 mm Hg, eGFR ≥ 30 mL/min/1.73 m² and serum K ≤ 5.4 mmol/L at randomization



Primary endpoint: Death from CV causes or hospitalization for HF

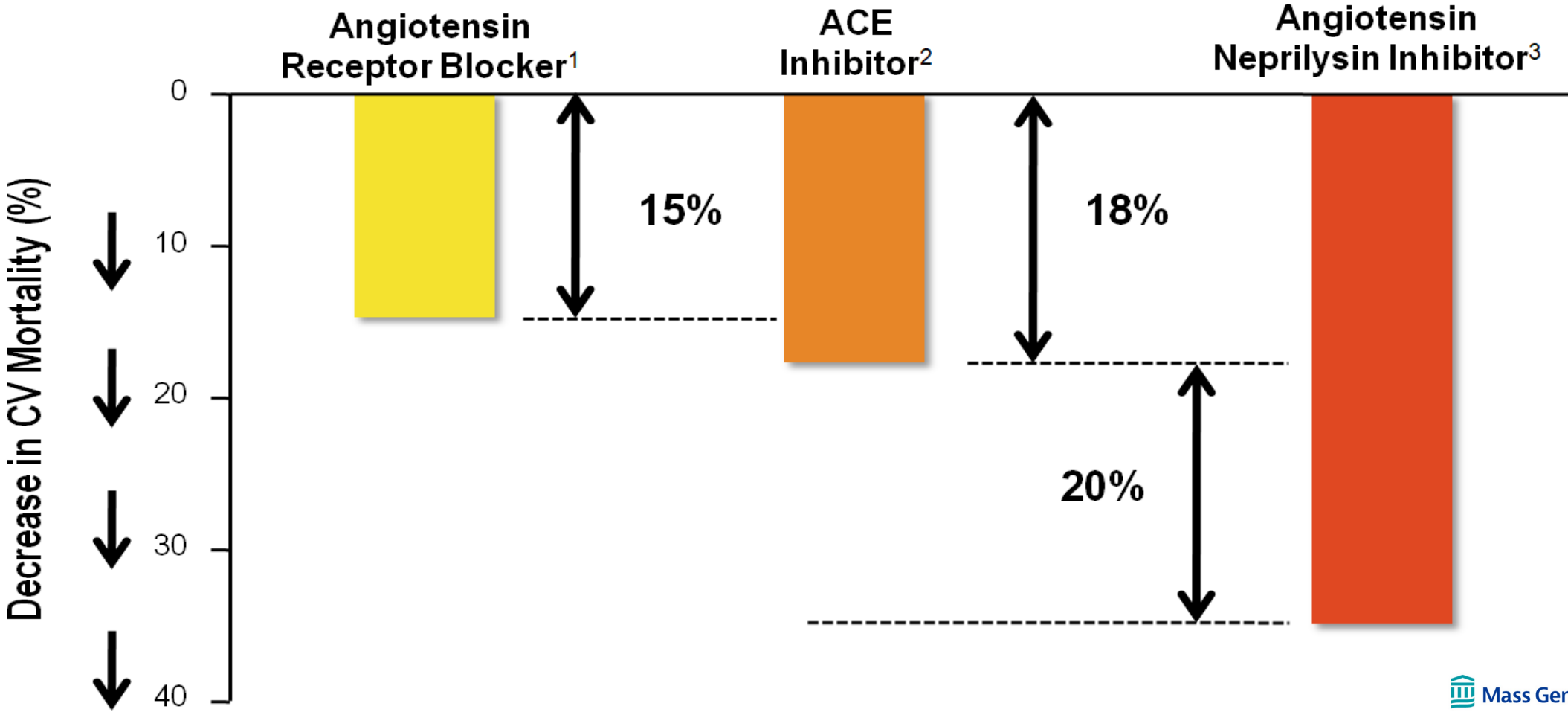
PARADIGM-HF: Primary Endpoint of CV Death or Heart Failure Hospitalization



Number at Risk

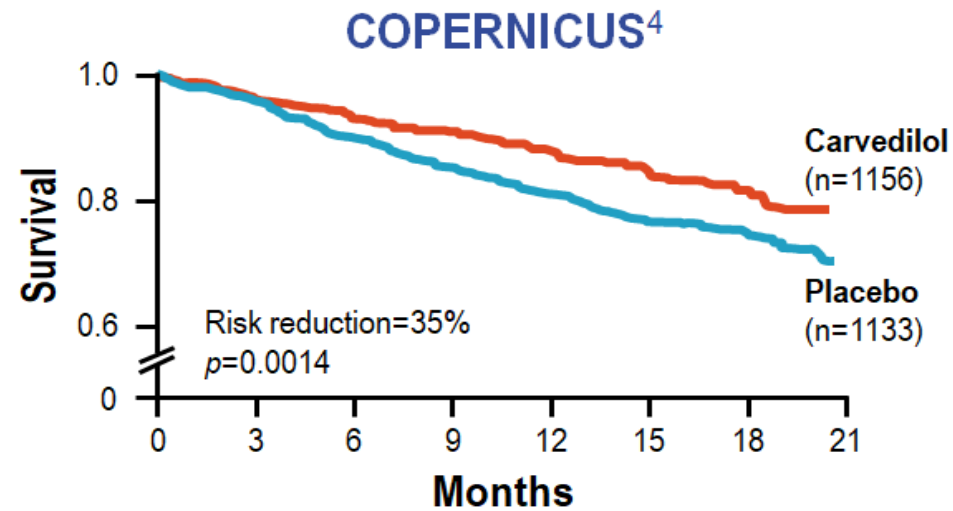
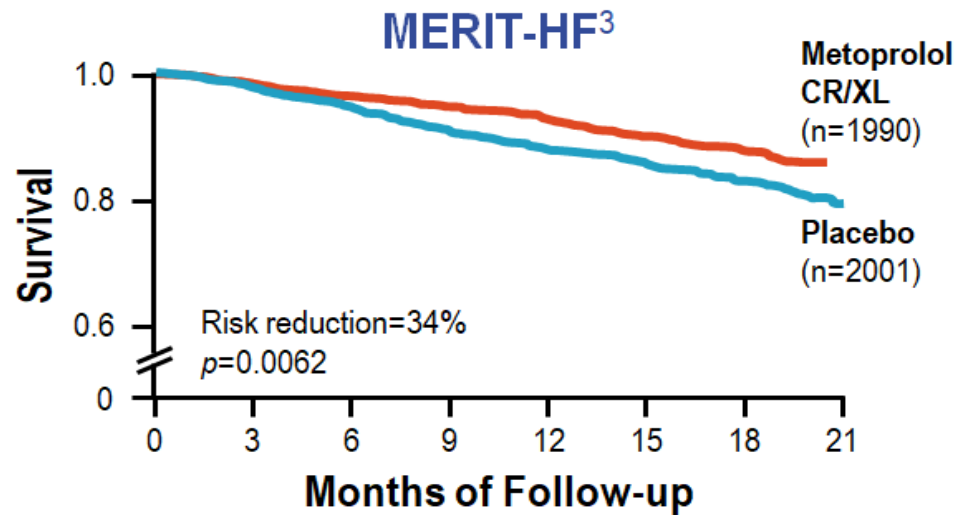
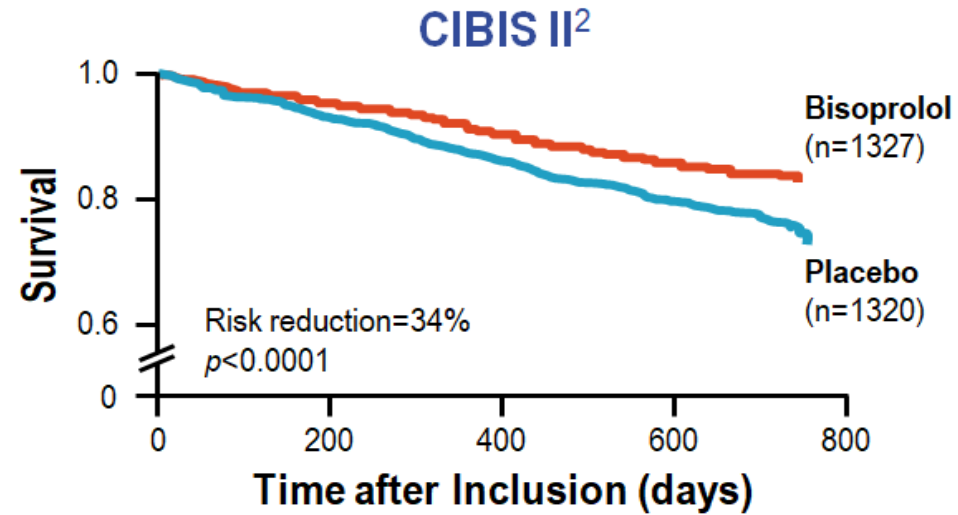
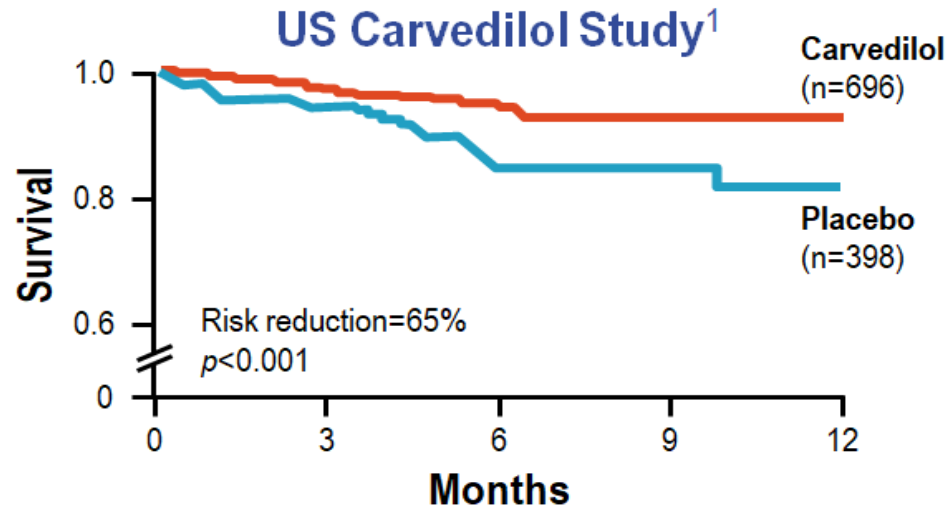
Sac/Val	4187	3922	3663	3018	2257	1544	896	249
Enalapril	4212	3883	3579	2922	2123	1488	853	236

Sac/Val Effect on CV Death in Addition to Current RAS Inhibitors



1. Granger CB et al. *Lancet*. 2003;362:772-776. 2. The SOLVD Investigators. *N Engl J Med*. 1991;325:293-302. 3. McMurray JJV et al. *N Engl J Med*. 2014;371:993-1004.

Beta-Blockers in Heart Failure



1. Packer M et al. *N Engl J Med*. 1996;334:1349-1355.
3. MERIT-HF Study Group. *Lancet*. 1999;353:2001-2007.

2. CIBIS II Investigators and Committees. *Lancet*. 1999;353:9-13.
4. Packer M et al. *Circulation*. 2001;344:1651-1658.

Not all Beta-Blockers Are Created Equal?

Beta-Blocker	Long-Term Effect
Bisoprolol ¹	Beneficial
Bucindolol ²	No effect
Carvedilol ³⁻⁵	Beneficial
Metoprolol tartrate ⁶	Not well studied
Metoprolol succinate ⁷	Beneficial
Nebivolol ⁸	No effect
Xamoterol ⁹	Harmful

1. CIBIS II Investigators and Committees. *Lancet*. 1999;353:9-13.

3. Colucci WS et al. *Circulation*. 1996;94:2800-2806.

5. The CAPRICORN Investigators. *Lancet*. 2001;357:1385-1390.

7. MERIT-HF Study Group. *Lancet*. 1999;353:2001-2007.

9. The Xamoterol in Severe Heart Failure Study Group. *Lancet*. 1990;336:1-6.

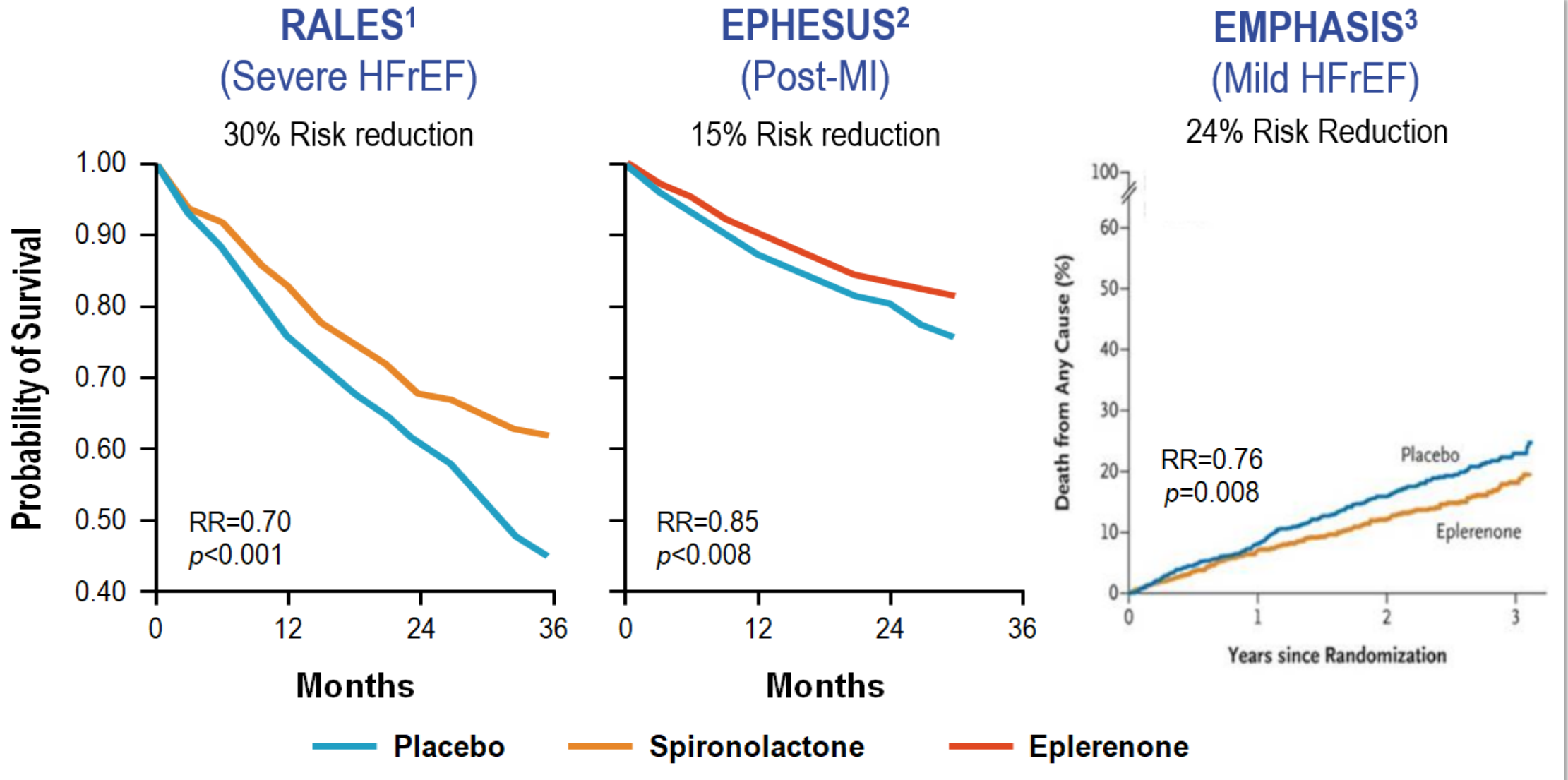
2. The BEST Investigators. *N Engl J Med*. 2001; 344:1659-1667.

4. Packer M et al. *N Engl J Med*. 2001;344:1651-1658.

6. Waagstein F et al. *Lancet*. 1993;342:1441-1446.

8. SENIORS Study Group. *Eur Heart J*. 2005; 26:215-225.

MRA in HF

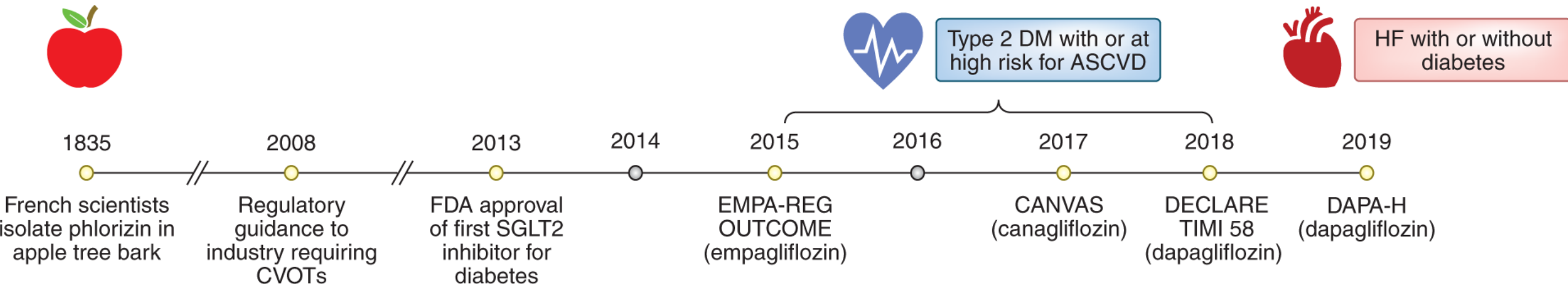


1. Pitt B et al. *N Engl J Med.* 1999;341:709-717.

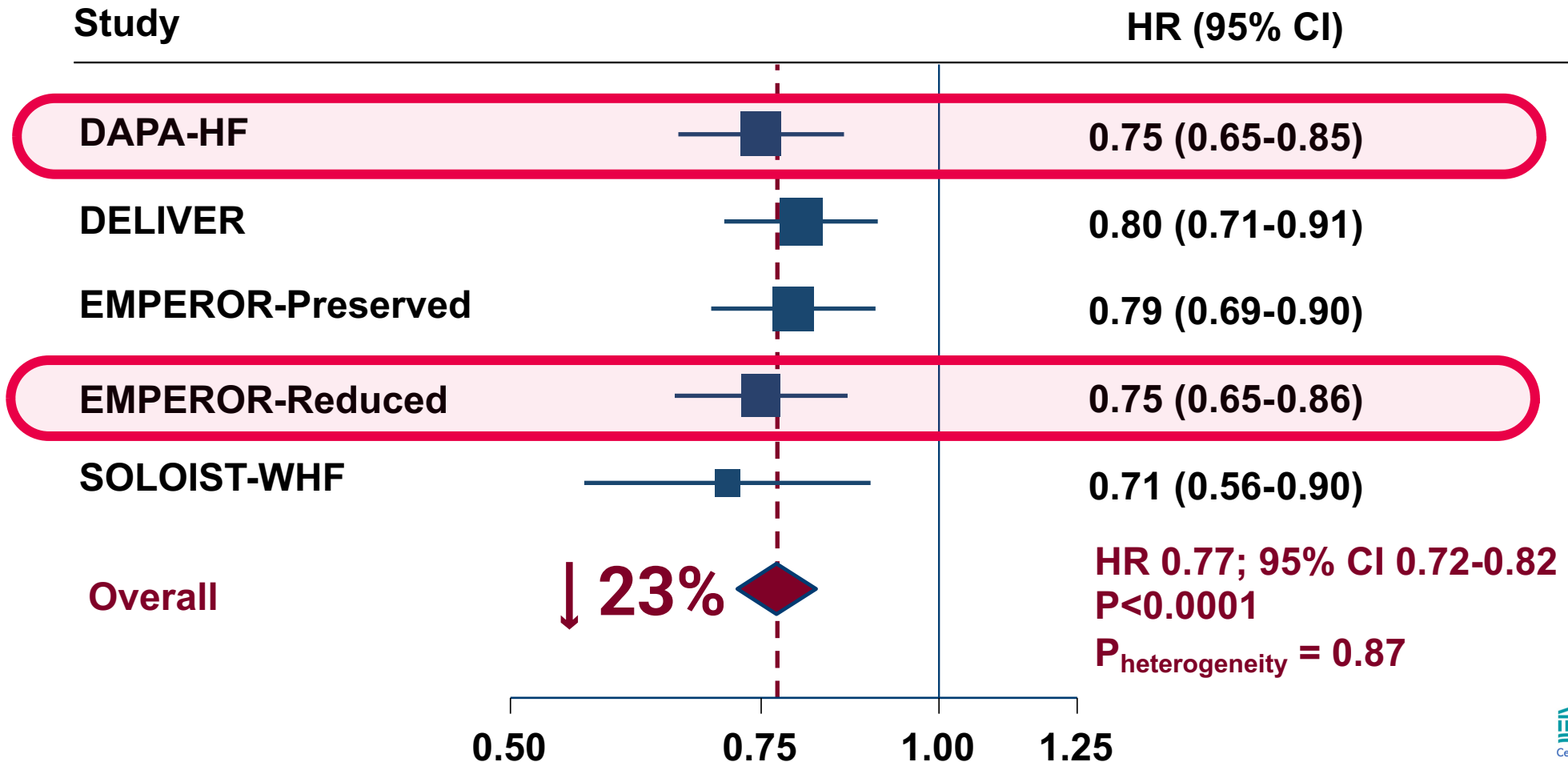
2. Pitt B et al. *N Engl J Med.* 2003;348:1309-1321.

3. Zannad F et al. *N Engl J Med.* 2011;364:11-21.

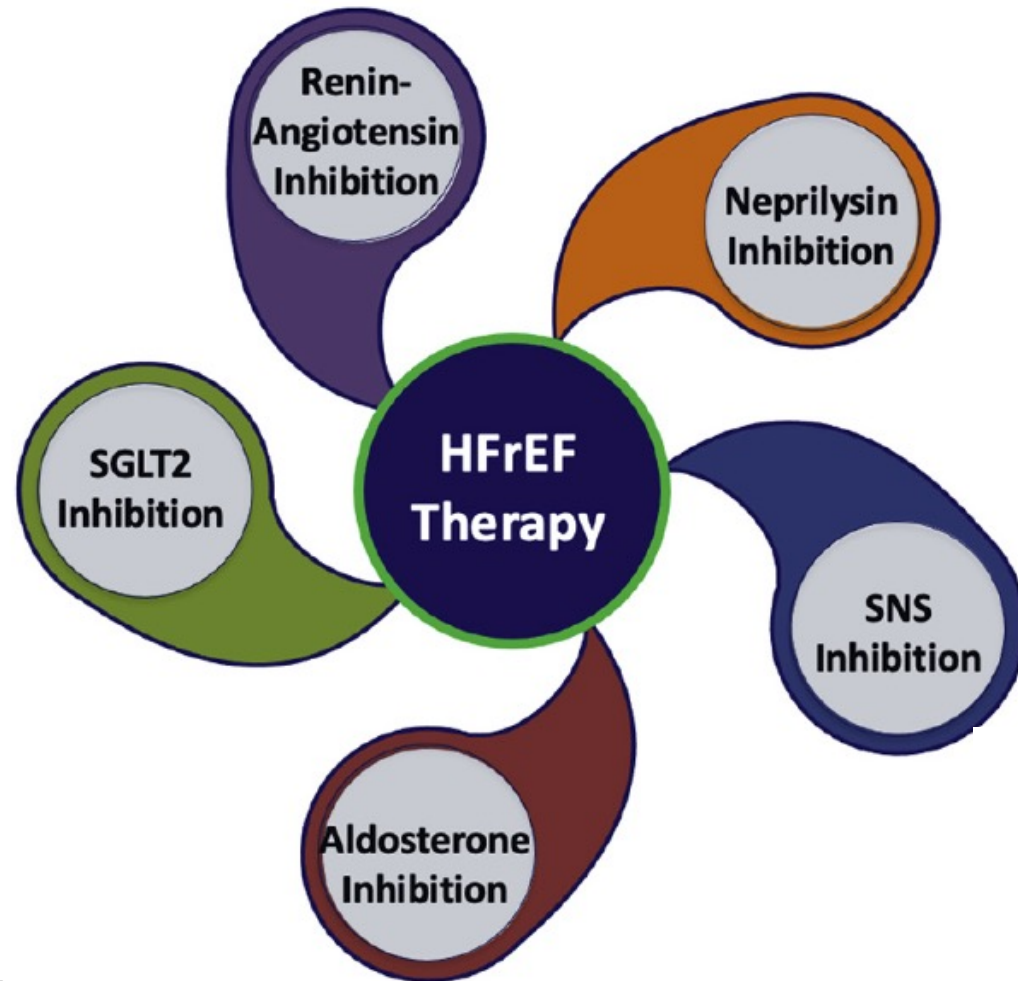
From HF Prevention to HF Treatment: The Discovery & Study of SGLT2i



Meta-Analysis of 5 Large Placebo-Controlled Trials: CV Death or HF Hosp

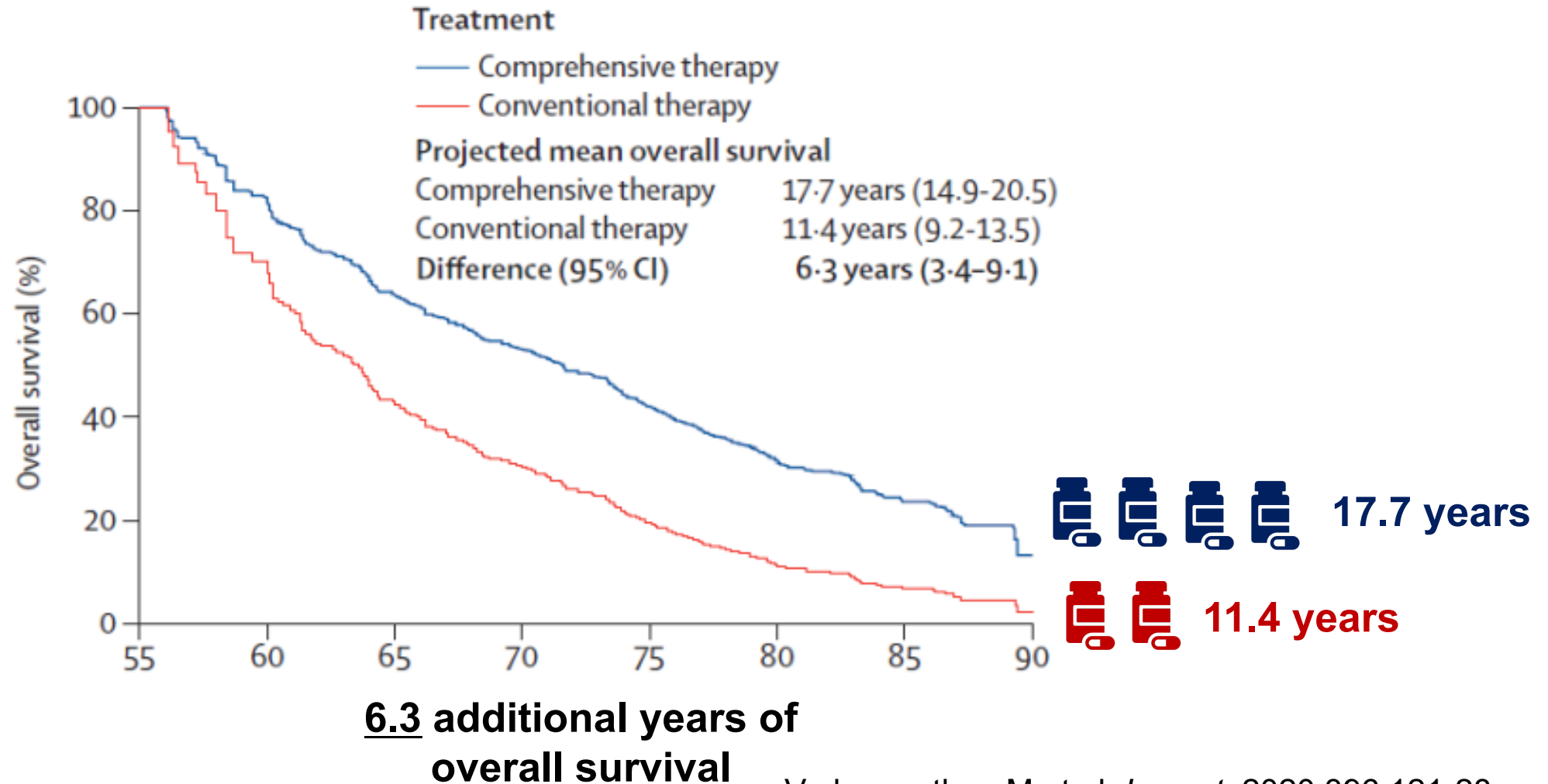


Heart Failure with Reduced Ejection Fraction



Bhatt AS et al. *J. Am. Coll. Cardiol. HF.* 2020.

Comprehensive Therapy (ARNI+BB+MRA+SGLT2i) vs. Conventional Therapy (ACEi/ARB + BB) in a 55-year-old patient with HFrEF



Practical Tips for Implementation



EXPERT CONSENSUS DECISION PATHWAY

2021 Update to the 2017 ACC Expert Consensus Decision Pathway for Optimization of Heart Failure Treatment: Answers to 10 Pivotal Issues About Heart Failure With Reduced Ejection Fraction

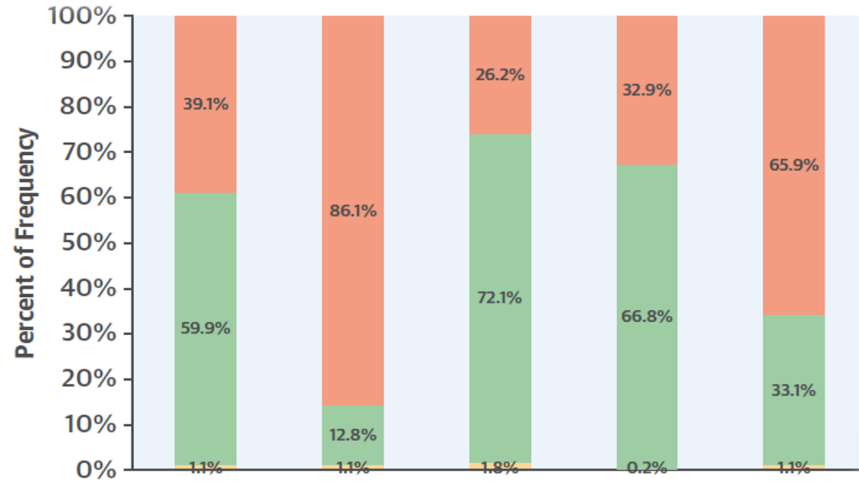


A Report of the American College of Cardiology Solution Set Oversight Committee

How are we doing? Persistent Implementation Gaps



2015-2017



	ACEI/ARB	ARNI	ACEI/ARB/ARNI	Beta-Blocker	MRA
Without Contraindication and Not Treated	1374	3029	920	1159	2317
Treated	2107	452	2536	2351	1163
With Contraindication	37	37	62	8	38



2020-2022

Patients 270,000 new users

Drug-naïve patients → hHF discharge → New use of GDMT (Initiation within 1 year of hHF discharge)

Aim
When are GDMTs initiated and how are they used?

After 100 Days

Initiation of novel GDMTs (dapagliflozin and sacubitril/valsartan) was delayed compared with other GDMTs, despite high CV death/hHF risks

Proportion of New GDMT Users Who Initiated Treatment Within 100 Days of hHF Discharge (%)

After 1 Year

After GDMT initiation, target dose achievement was often low, while discontinuation rates were high

Dapagliflozin

Sacubitril/Valsartan

ACE inhibitor

ARB

MRA

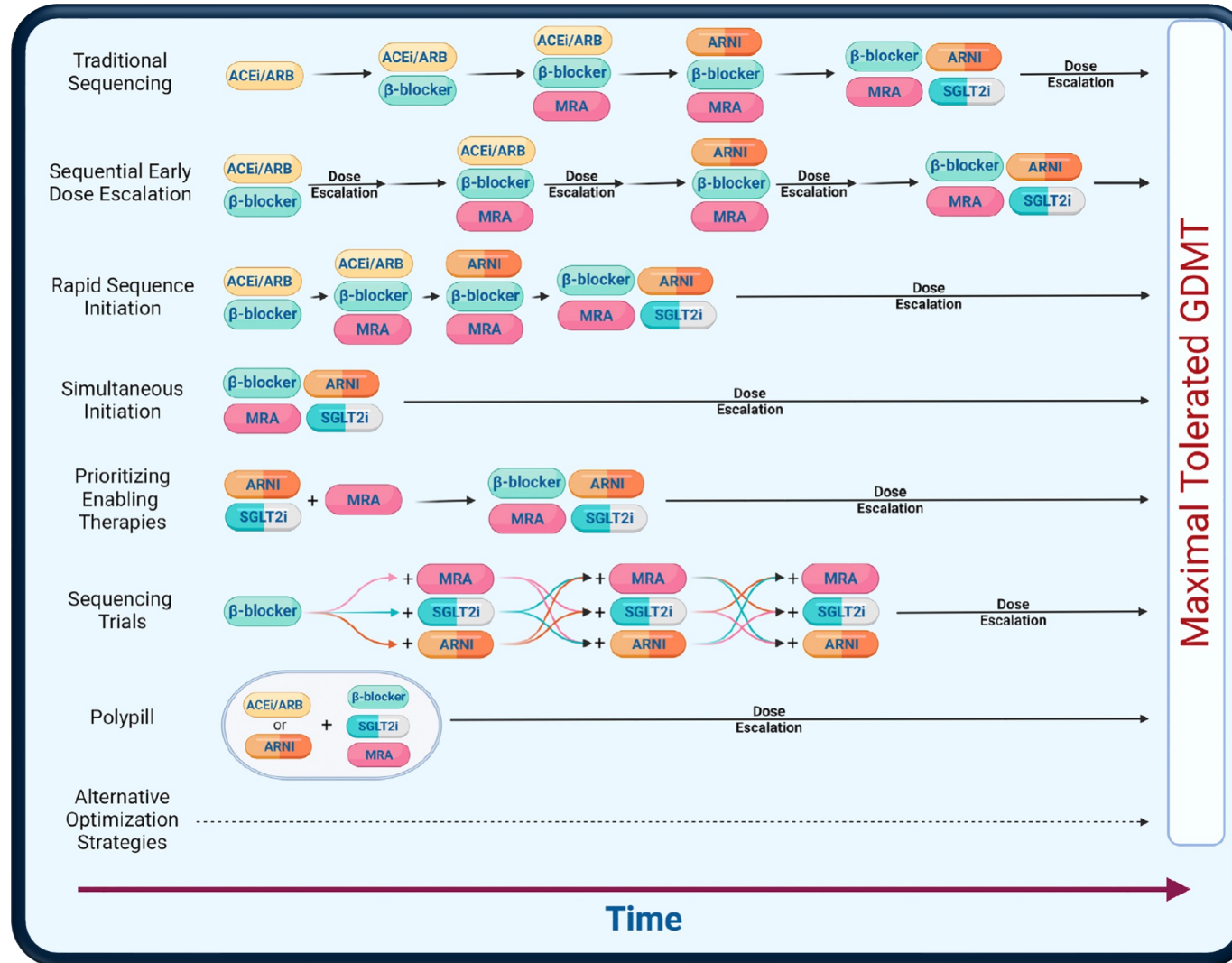
BB

Legend: Discontinued (red), Switch to sacubitril/valsartan (blue), Start dose (orange), Low dose (yellow), Intermediate dose (green), Target dose (dark green)

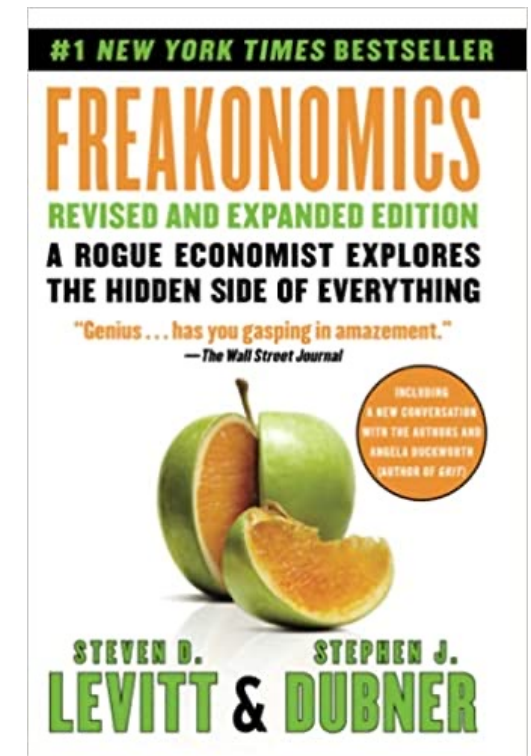
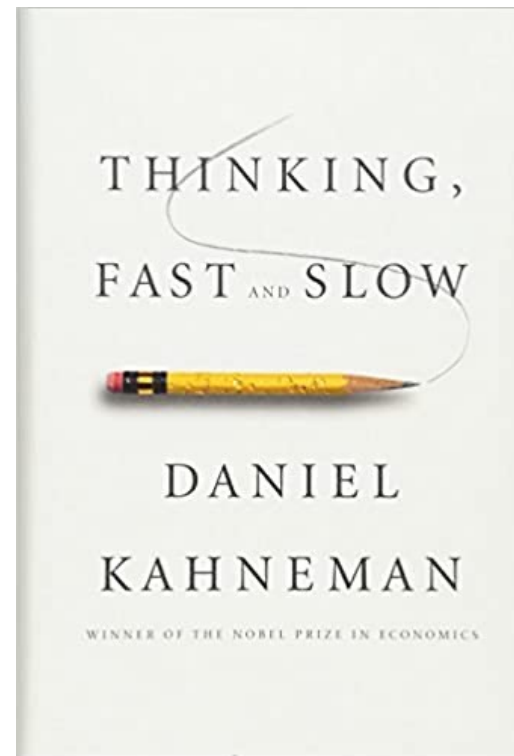
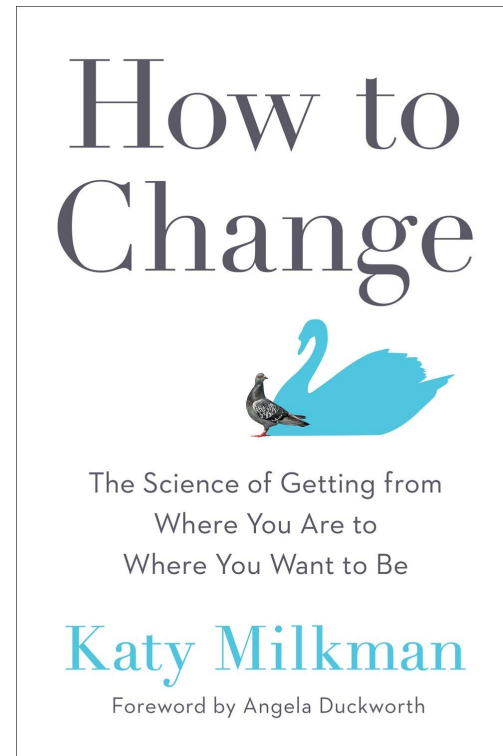
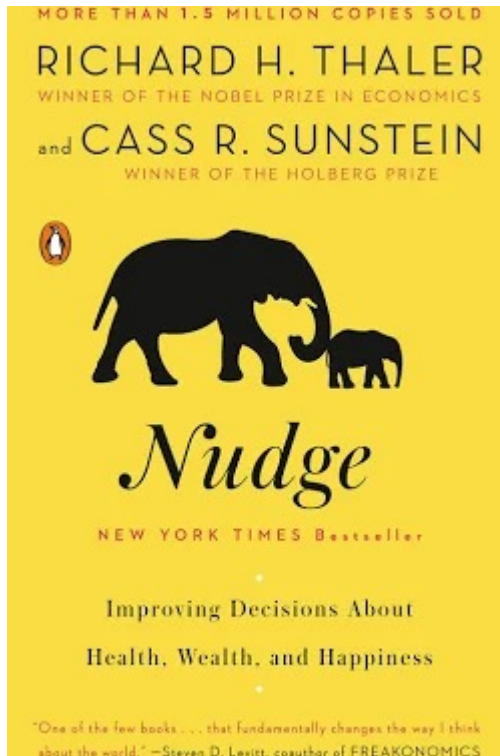
<5% of patients are on optimal guideline recommended HF therapy

Green SJ et al. *JACC-HF*. 2019.
Savarese G et al. *JACC-HF*. 2023.

Implementation Science in Cardiometabolic Care

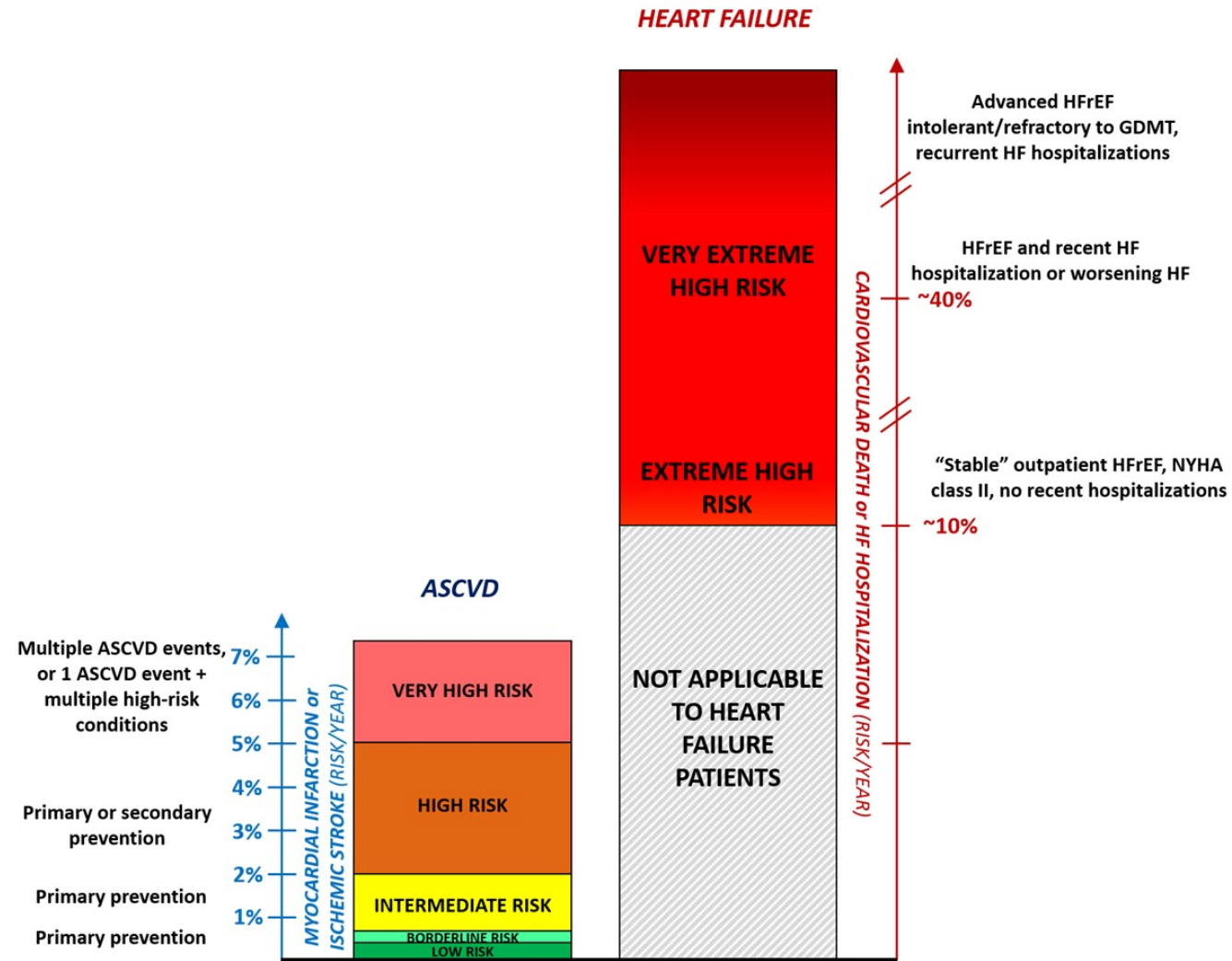


Behavioral nudges increasingly embraced by the public at large



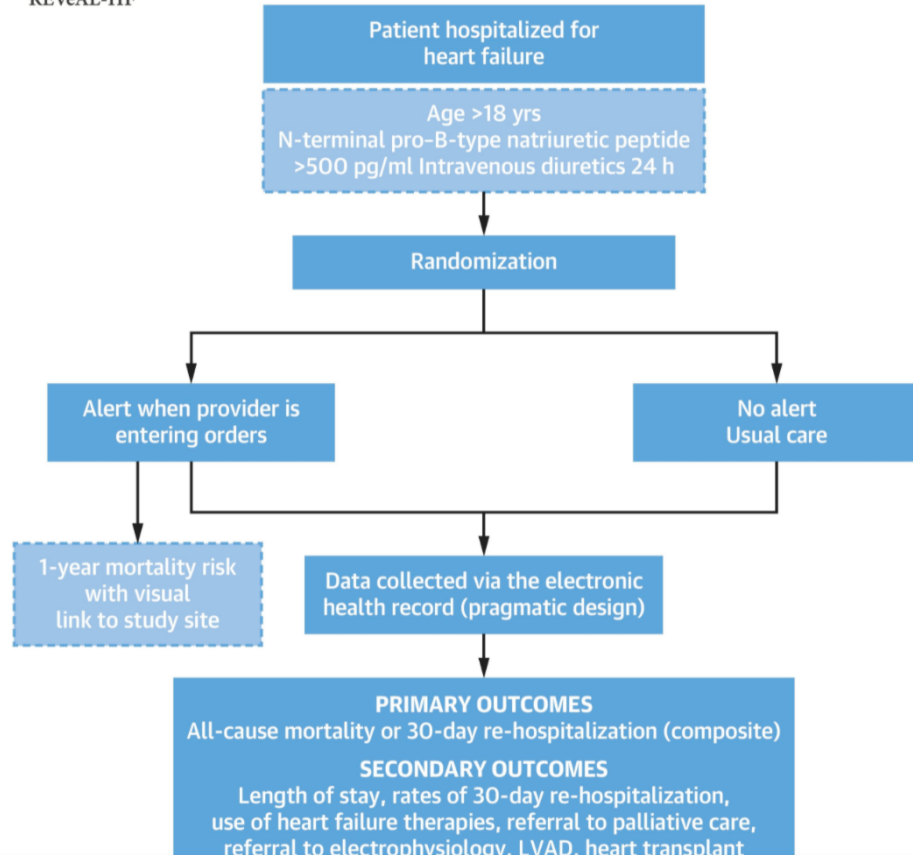
A nudge, by design, is a subtle change in design that can have an outsize impact on human behavior without limiting choice

Clinical Risk in Heart Failure

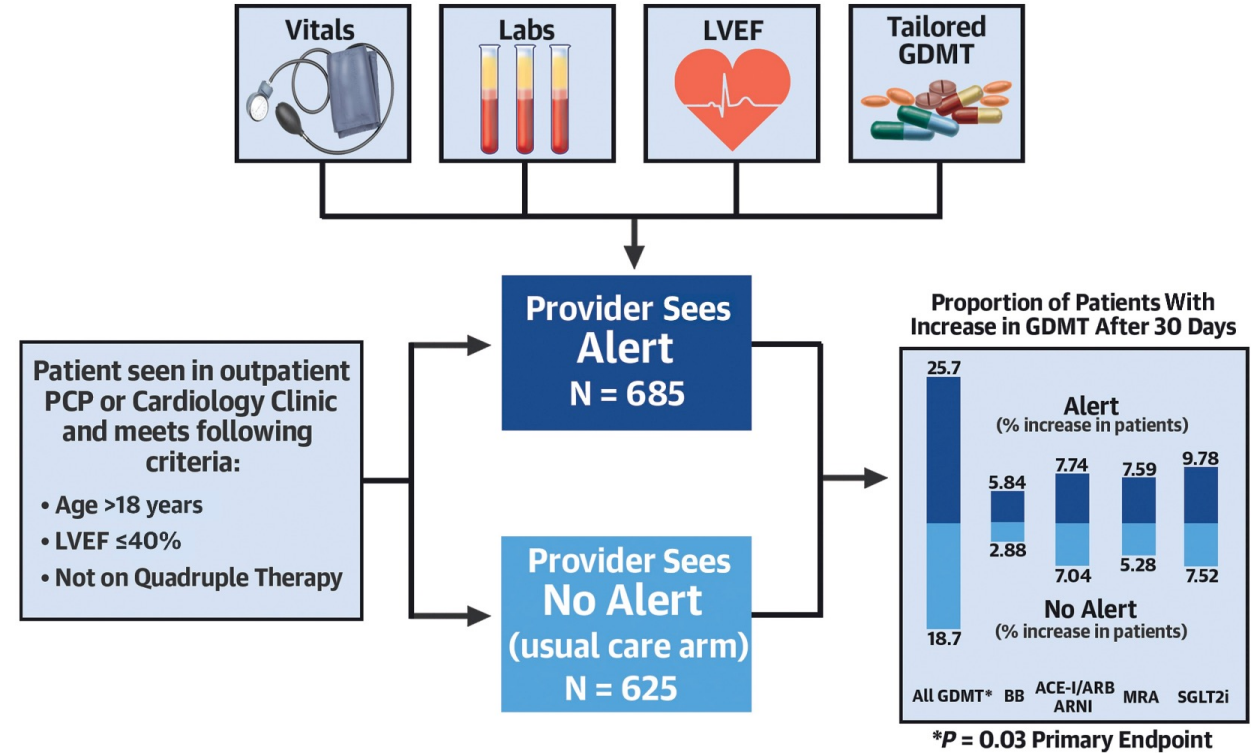


Greene S et. al. JAMA. 2021

Provider nudges in integrated health systems



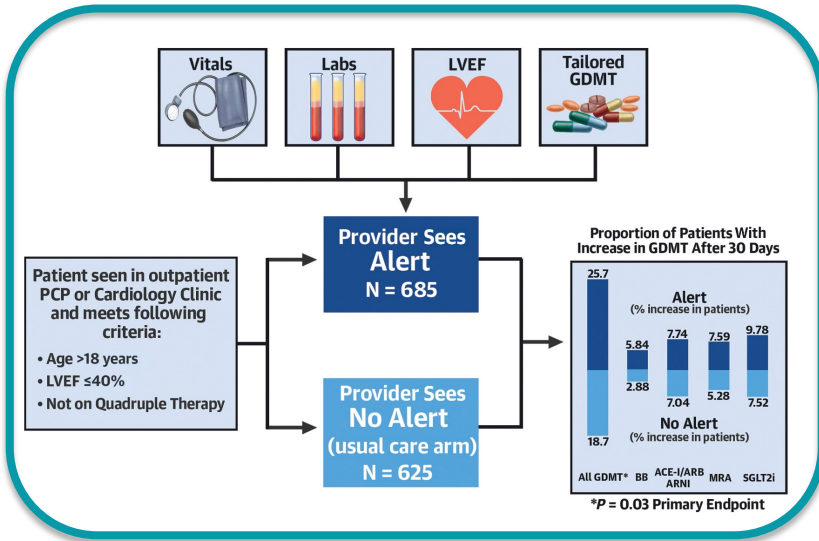
Risk Transparency
No change in outcomes



Clinical Decision Support
Modest improvement in implementation

Implementation Science in Heart Failure

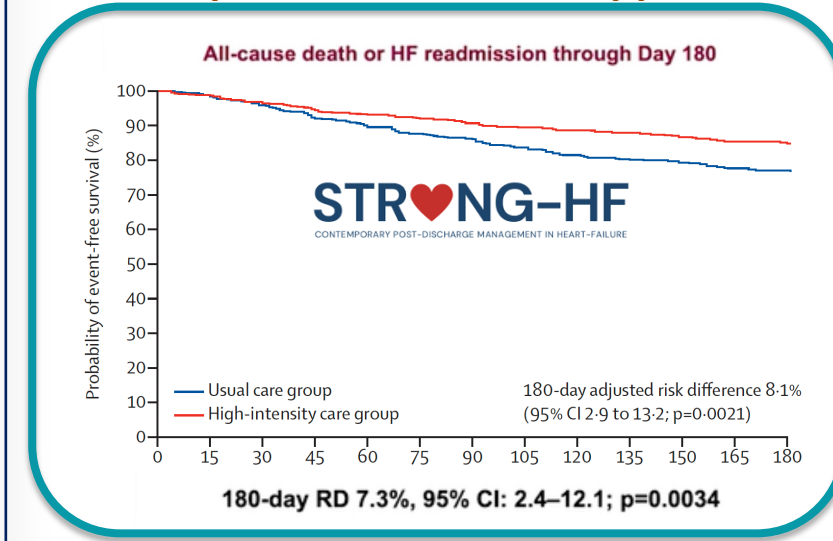
EHR-Based Clinical Decision Support



Highly Scalable
Modest Effect Size; ?Alert Fatigue



In-person care team support



Resource Intensive
Large Effect Size

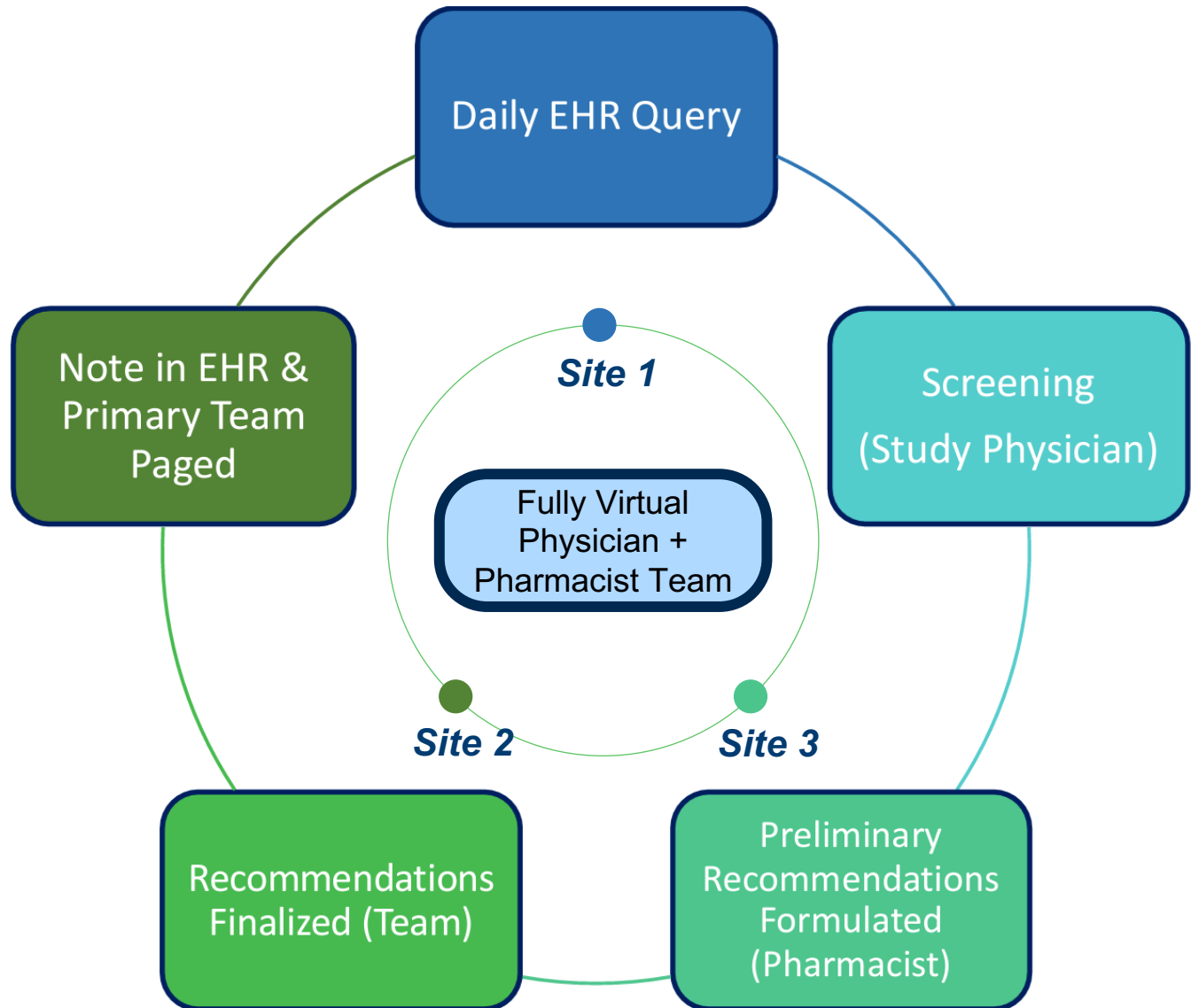
Rationale for the IMPLEMENT-HF Program

- Despite strong evidence and endorsement by clinical practice guidelines, implementation of medical therapy for HFrEF remains incomplete.
- Hospitalization, regardless of admission indication, may represent a potentially attractive setting for therapeutic optimization.
- Prior HF implementation trials have generally excluded two populations (1) patients admitted for non-HF reasons and (1) those with *de novo* presentations of HFrEF.

Hospitalization = Opportunity for GDMT Optimization

- Targets **high-risk** patients in a **well-resourced** setting
- Addresses potential reasons for poor outpatient GDMT optimization (time, reinforcement, education)
- Allows for frequent **hemodynamic** and symptom **monitoring**
- Can include patients hospitalized **for and with** HFrEF
- Potential for **virtual nudging strategies** to allow for scale across integrated health systems.

IMPLEMENT-HF: Virtual Care Team Guided Strategy



Facilitate **combination disease-modifying HF therapy:**

- ▲ Evidence-based β -Blocker
- ▲ ARNI > ACEI or ARB
- ▲ MRA
- ▲ SGLT2i

Up-titrate to target doses

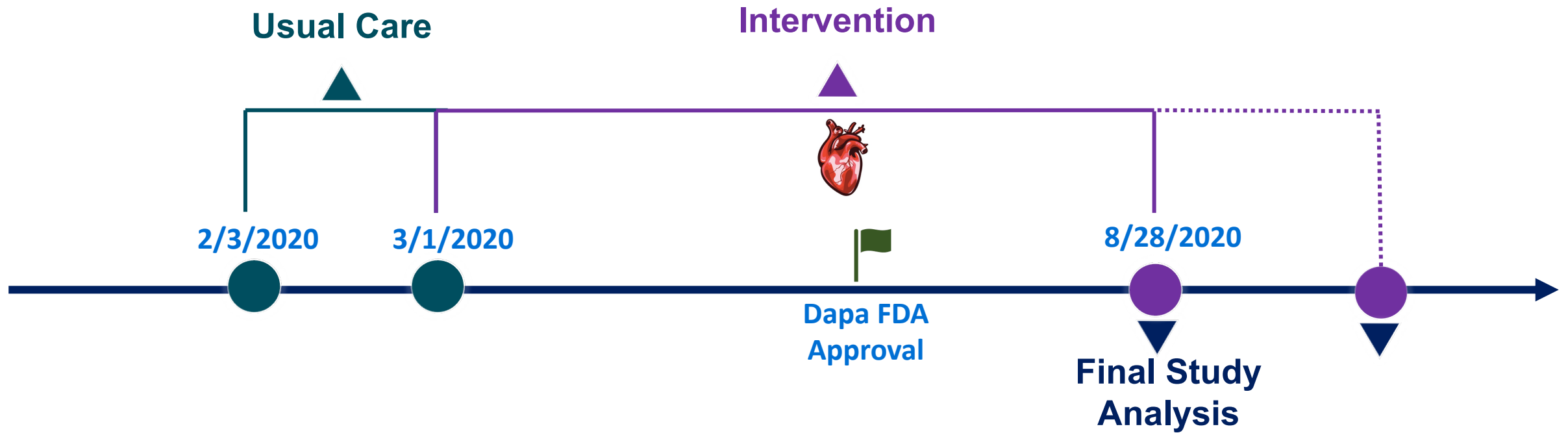
IMPLEMENT-HF Pilot Feasibility Study



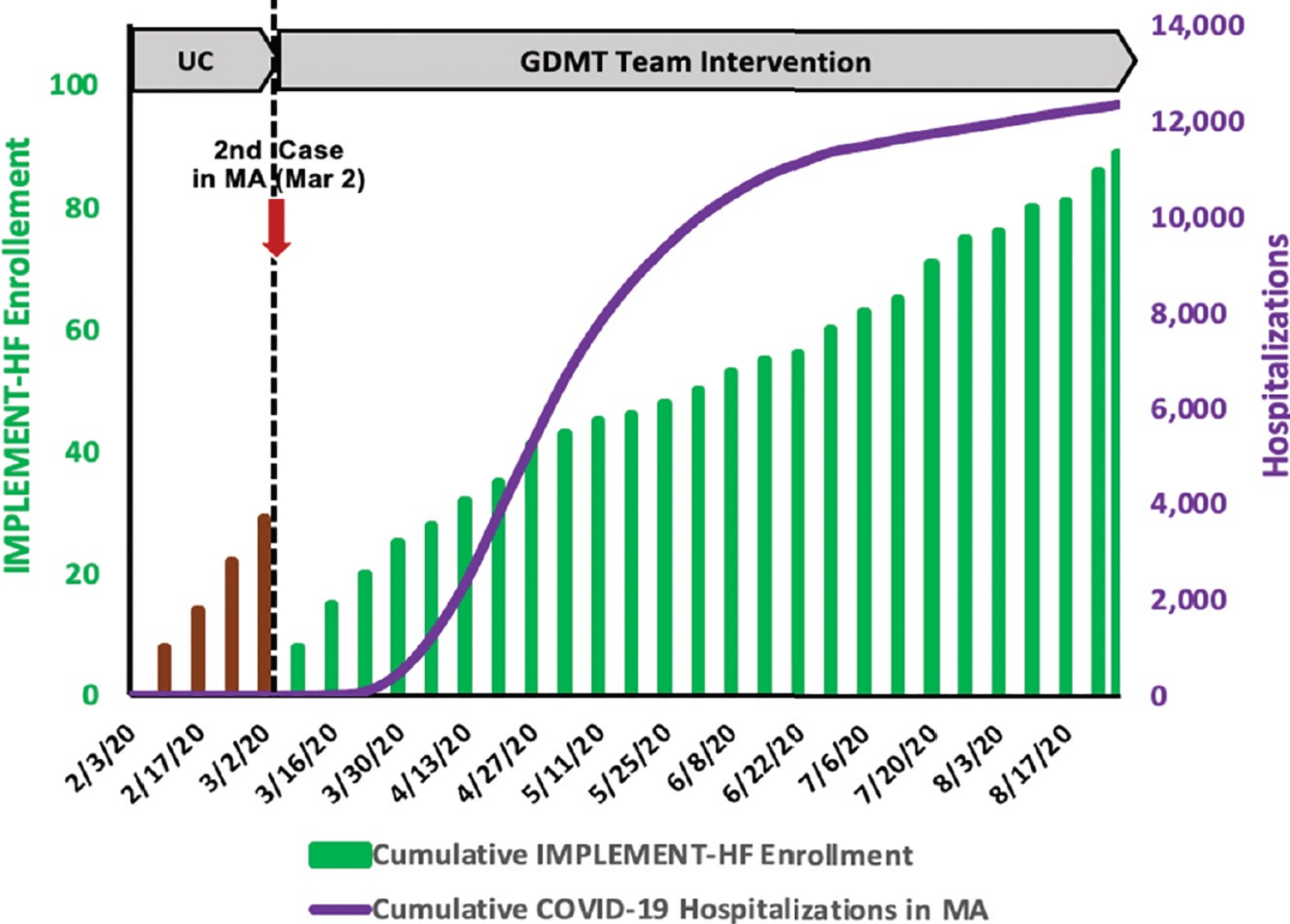
Virtual optimization of guideline-directed medical therapy in hospitalized patients with heart failure with reduced ejection fraction: the IMPLEMENT-HF pilot study

Ankeet S. Bhatt^{1†}, Anubodh S. Varshney^{1†}, Mahan Nekoui², Alea Moscone³, Jonathan W. Cunningham¹, Karola S. Jering¹, Parth N. Patel³, Lauren E. Sinnenberg³, Thomas D. Bernier⁴, Leo F. Buckley⁴, Bryan M. Cook⁴, Jillian Dempsey⁴, Julie Kelly⁴, Danielle M. Knowles⁴, Kenneth Lupi⁴, Rhynn Malloy⁴, Lina S. Matta⁴, Megan N. Rhoten⁴, Krishan Sharma⁵, Caroline A. Snyder⁶, Clara Ting⁴, Erin E. McElrath³, Mary G. Amato^{3,7}, Maryam Alobaidly⁸, Catherine E. Ulbricht^{7,8}, Niteesh K. Choudhry⁹, Dale S. Adler^{1,3}, and Muthiah Vaduganathan^{1*}

IMPLEMENT-HF Pilot Feasibility Study

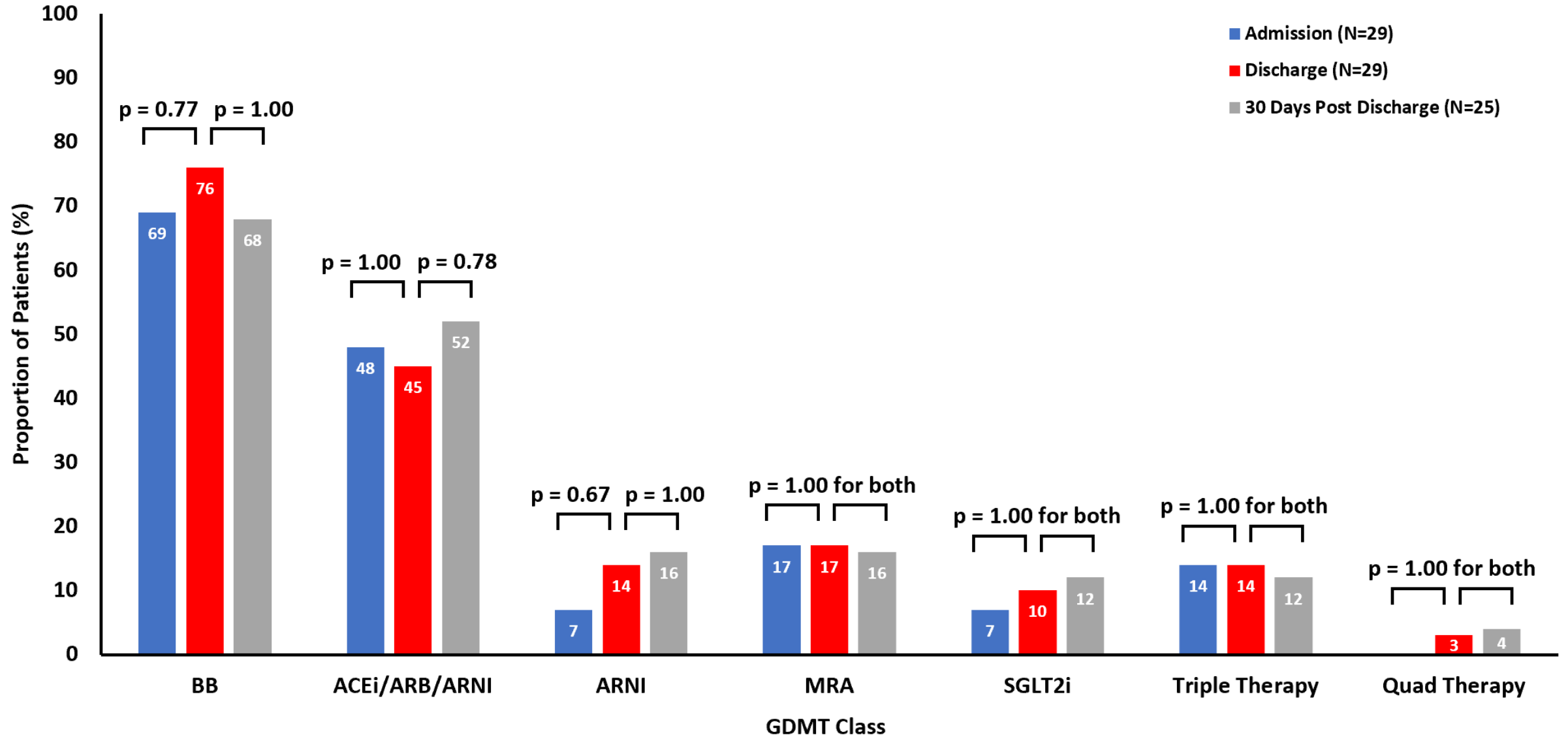


IMPLEMENT-HF Pilot Feasibility Study

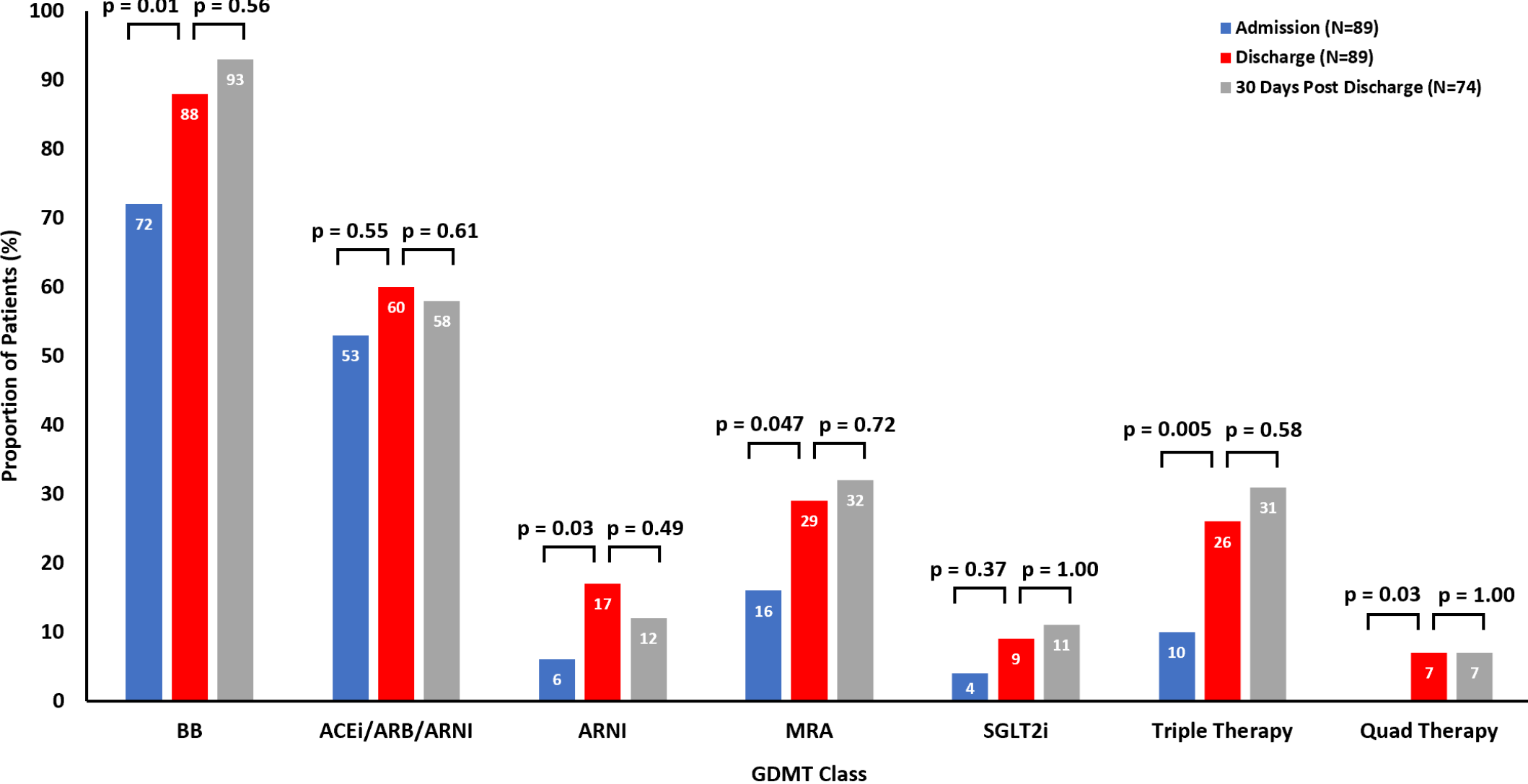


Bhatt AS, Varshney AS et. al. Eur J Heart Failure. 2021.

IMPLEMENT-HF Pilot: Usual Care

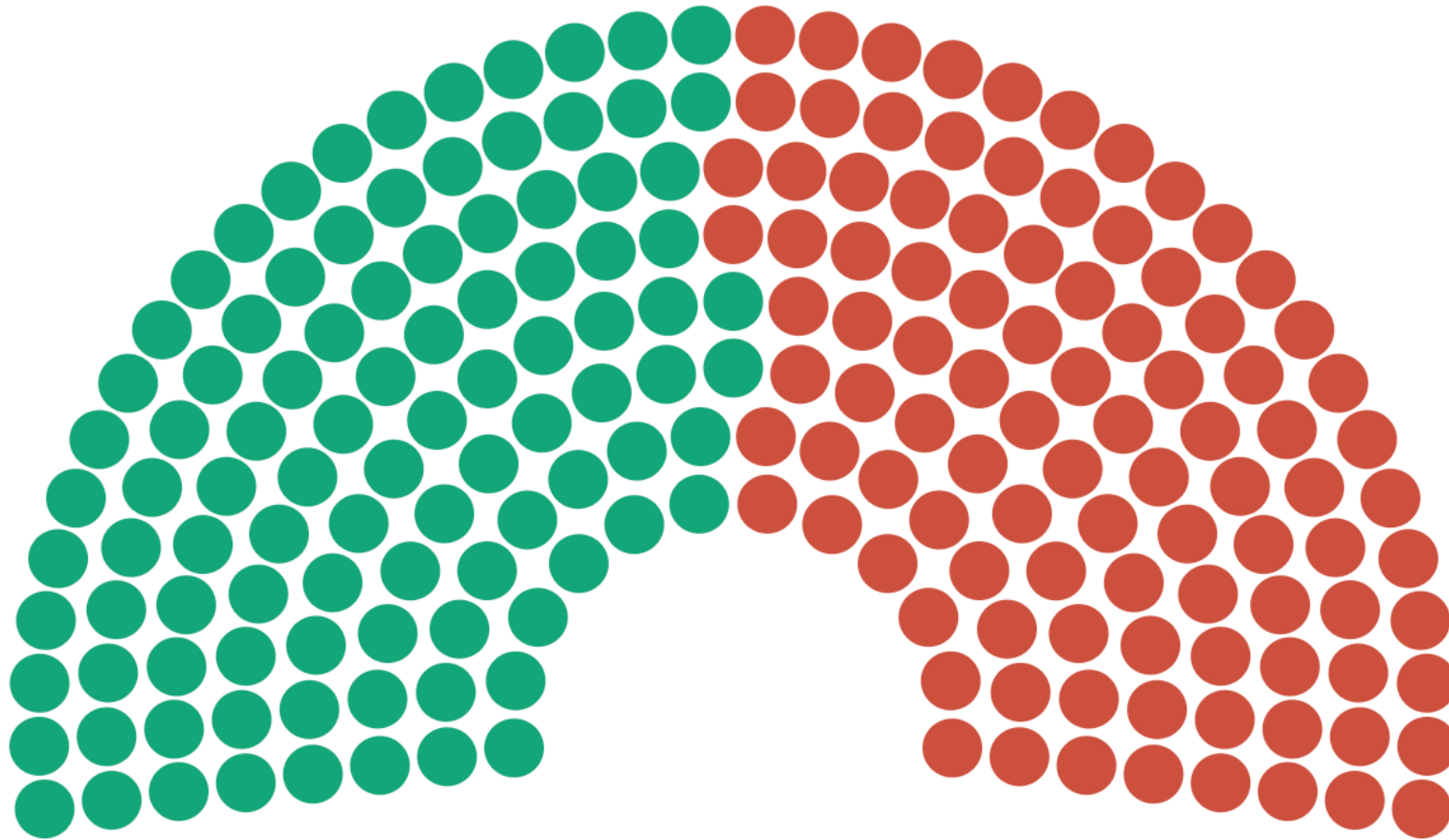


IMPLEMENT-HF Pilot: Intervention



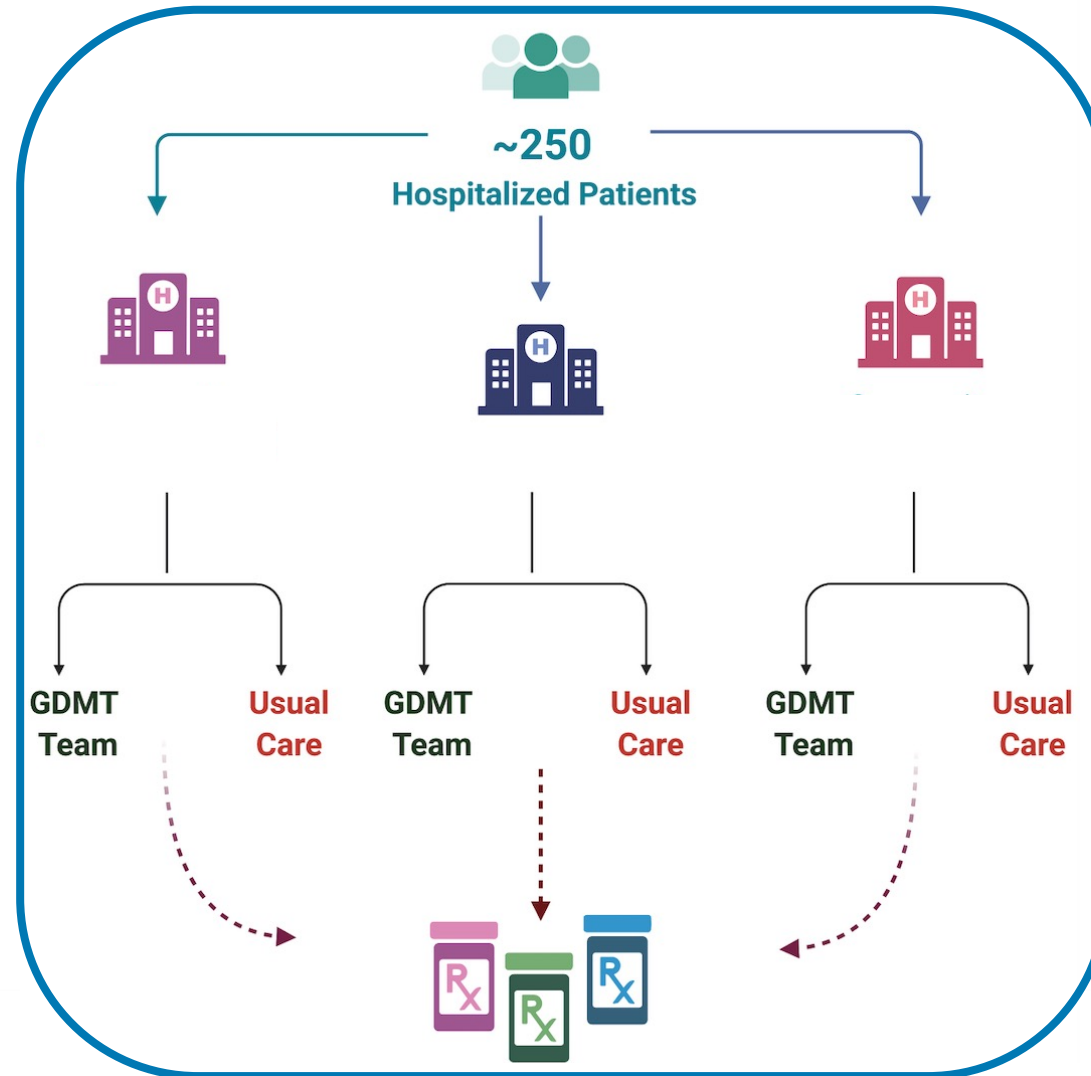
Bhatt AS, Varshney AS et. al. Eur J Heart Failure. 2021.

IMPLEMENT-HF Pilot: Recommendations



- Implemented (N=100, 50%)
- Not Implemented (N=100, 50%)

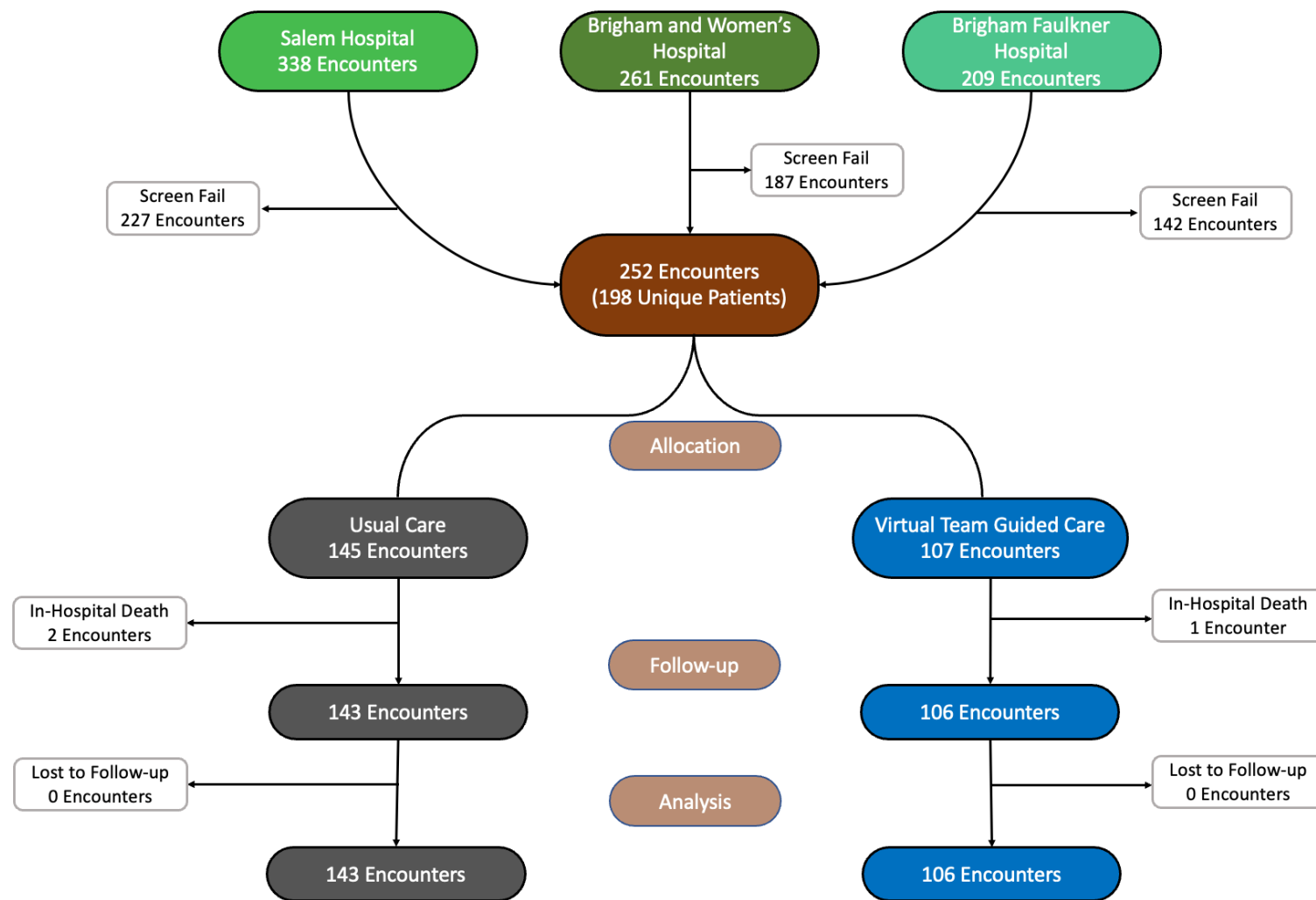
The IMPLEMENT-HF Pivotal Study



Inclusion & Exclusion Criteria

Inclusion Criteria	Exclusion Criteria
Age \geq 18 years	Received care in an intensive care unit
LVEF \leq 40% assessed in preceding 12 months	Admission to a same-day procedural or surgical service
Admitted to a participating facility on a non-intensive care unit medical or surgical service	Inotropic or mechanical circulatory support use
	Acute coronary syndrome, percutaneous cardiac procedure, stroke, or major cardiovascular vascular surgery within 30 days
	Systolic blood pressure $<$ 90 mmHg in the preceding 24 hours
	Severe valvular disease or \geq moderate RV dysfunction on most recent TTE
	Pulmonary hypertension on disease specific therapies
	Congenital heart disease
	Amyloid heart disease
	Hypertrophic or restrictive cardiomyopathy
	Bacteremia or suspected bacteremia
	History of or listed for any solid organ transplant
	Admission for bone marrow transplant or chemotherapy administration
	Receiving hospice care or comfort-measures only
	Admission for COVID-19
	Pregnant or nursing women
	Physician discretion

Design of the IMPLEMENT-HF Pivotal Study



Effectiveness Outcomes:

- Composite In-hospital GDMT Optimization Score
- Proportion of encounters with HF therapy intensification

Adjudicated Safety Outcomes:

- Acute kidney Injury
- Hyperkalemia
- Bradycardia
- Hypotension

Select Baseline Characteristics

	Virtual Care Team Strategy n=107	Usual Care n=145
<i>Demographics</i>		
Age (years)	70 ± 12	69 ± 15
Women	35%	33%
Race		
White	78%	71%
Black	13%	15%
Other	9%	14%
Hispanic ethnicity	17%	18%
Primary language		
English	87%	85%
Spanish	14%	11%
Other	0%	4%
Primary admission diagnosis of heart failure	25%	24%
De-novo presentation of HF	22%	18%
Left ventricular ejection fraction (%)	33 ± 9	32 ± 9
Coronary artery disease	48%	49%
Cancer	17%	17%
Diabetes mellitus	47%	39%
<i>Admission Vital Signs and Laboratory Measures</i>		
Systolic blood pressure (mmHg)	134 ± 29	132 ± 25
Heart rate (bpm)	88 ± 21	89 ± 23
Sodium (mEq/L)	138 ± 4	137 ± 4
Potassium (mEq/L)	4.2 ± 0.6	4.3 ± 0.7
eGFR (mL/min/1.73m ²)	61 ± 31	62 ± 32

Bhatt AS, Varshney AS et al. J Am Coll Cardiol. 2023.

Primary Endpoint

In-hospital GDMT

Optimization Score:

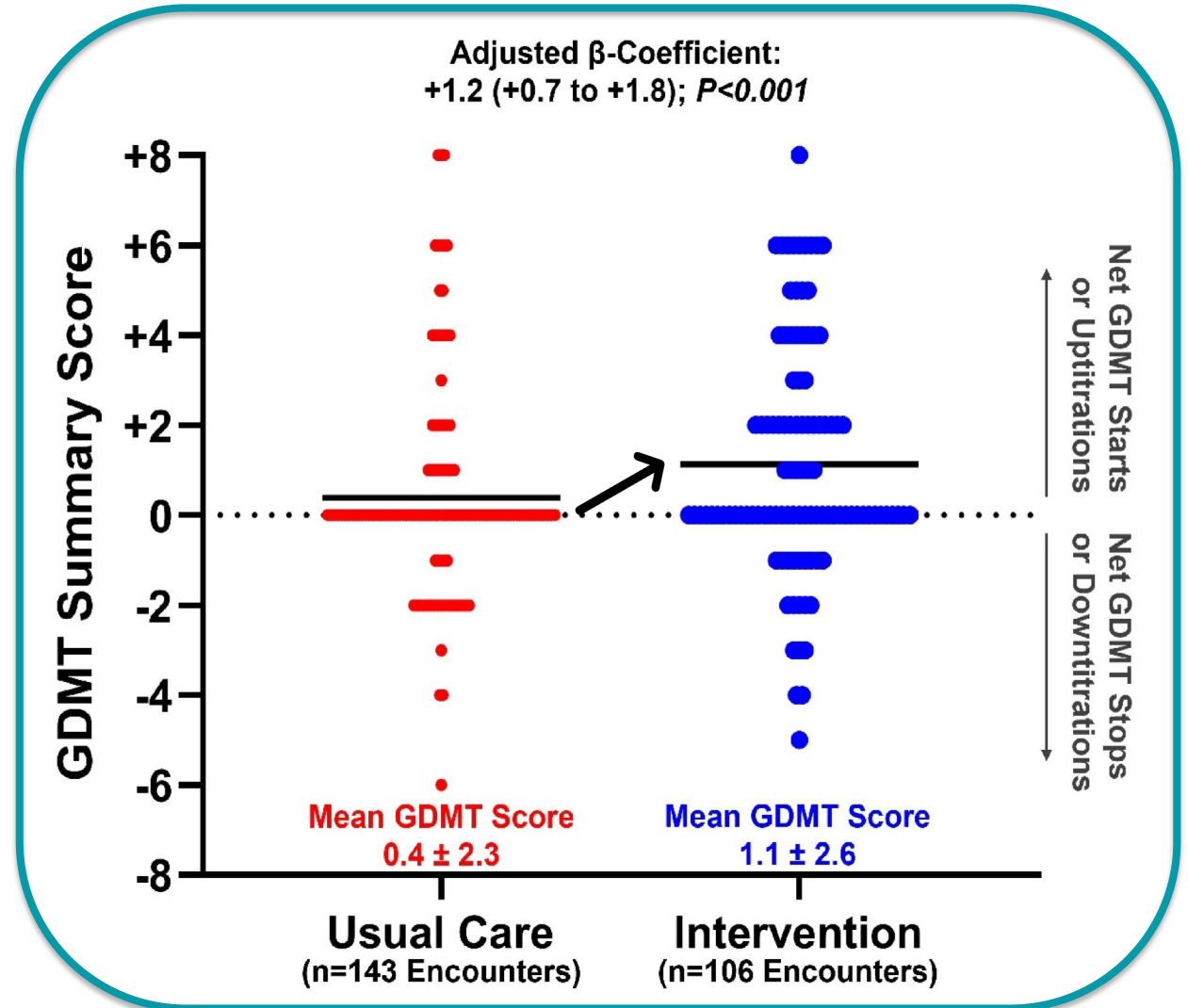
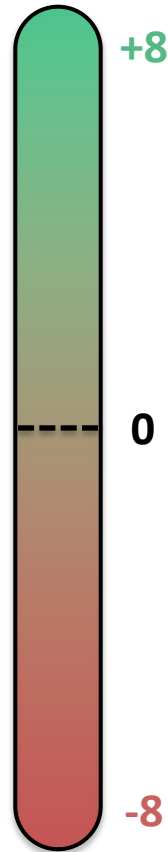
+2 for new initiations

+1 for dose ↑↑

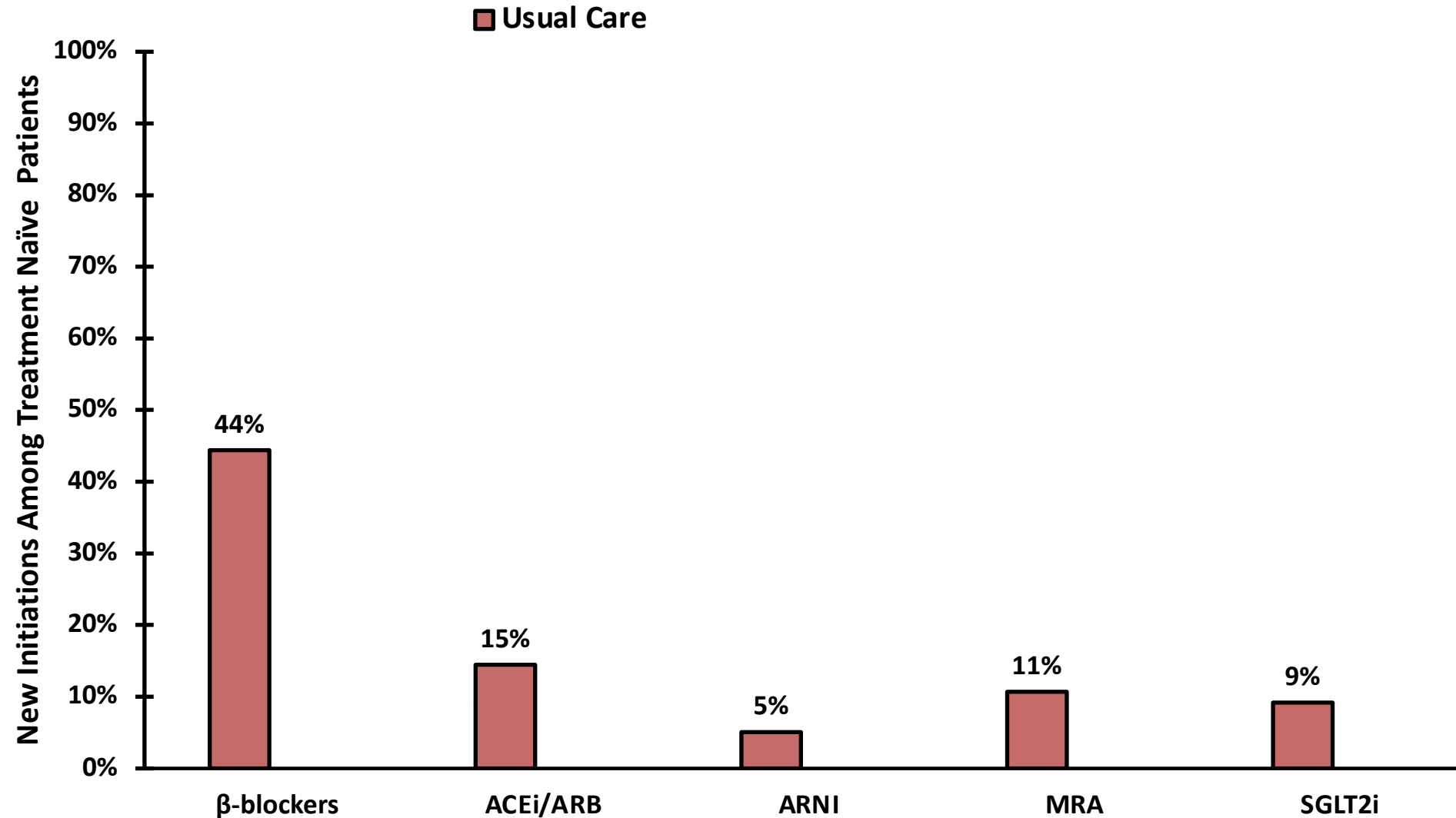
-1 for dose ↓↓

-2 for new discontinuations

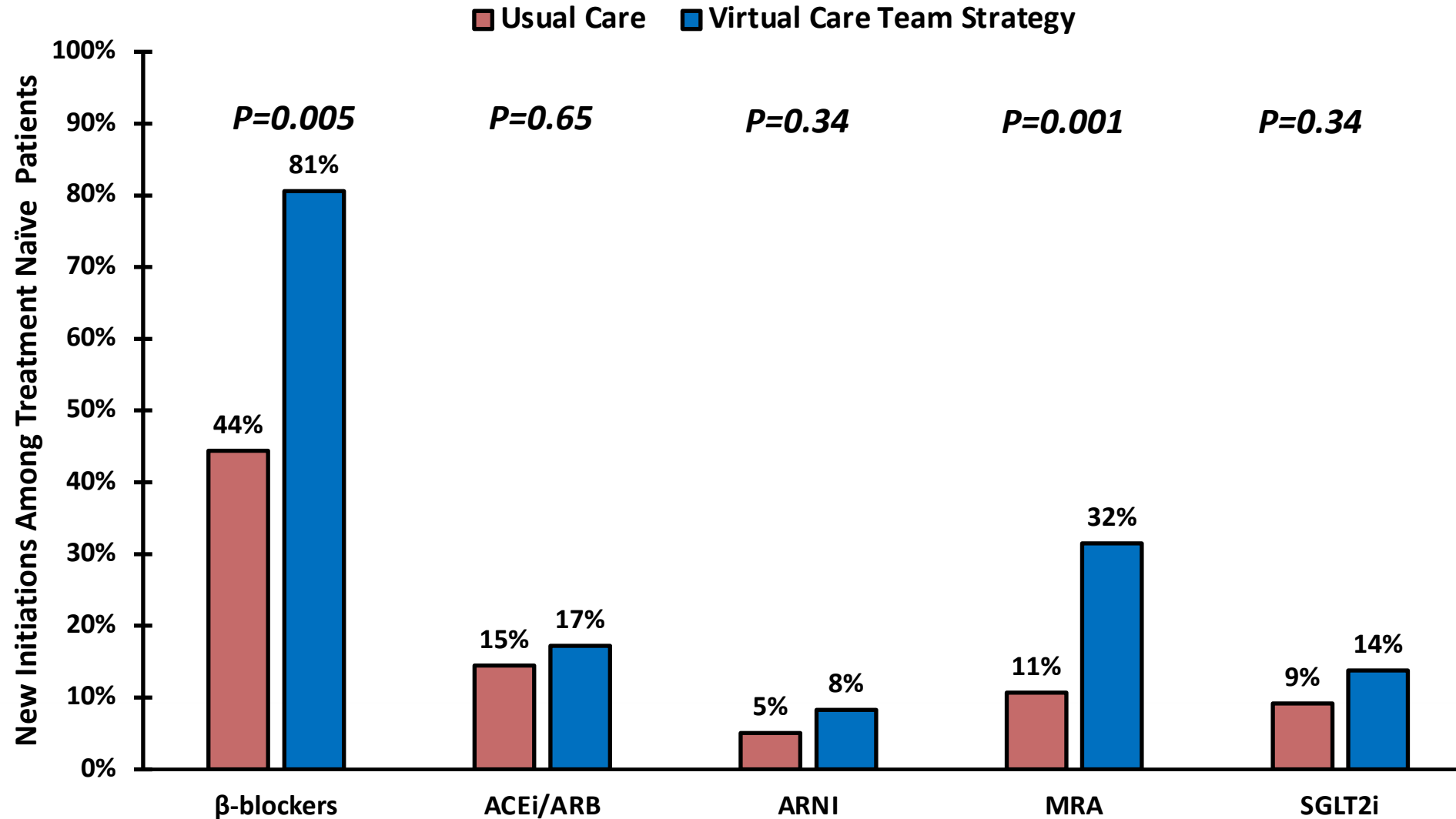
Assessed by comparing prior to admission and discharge medication regimens



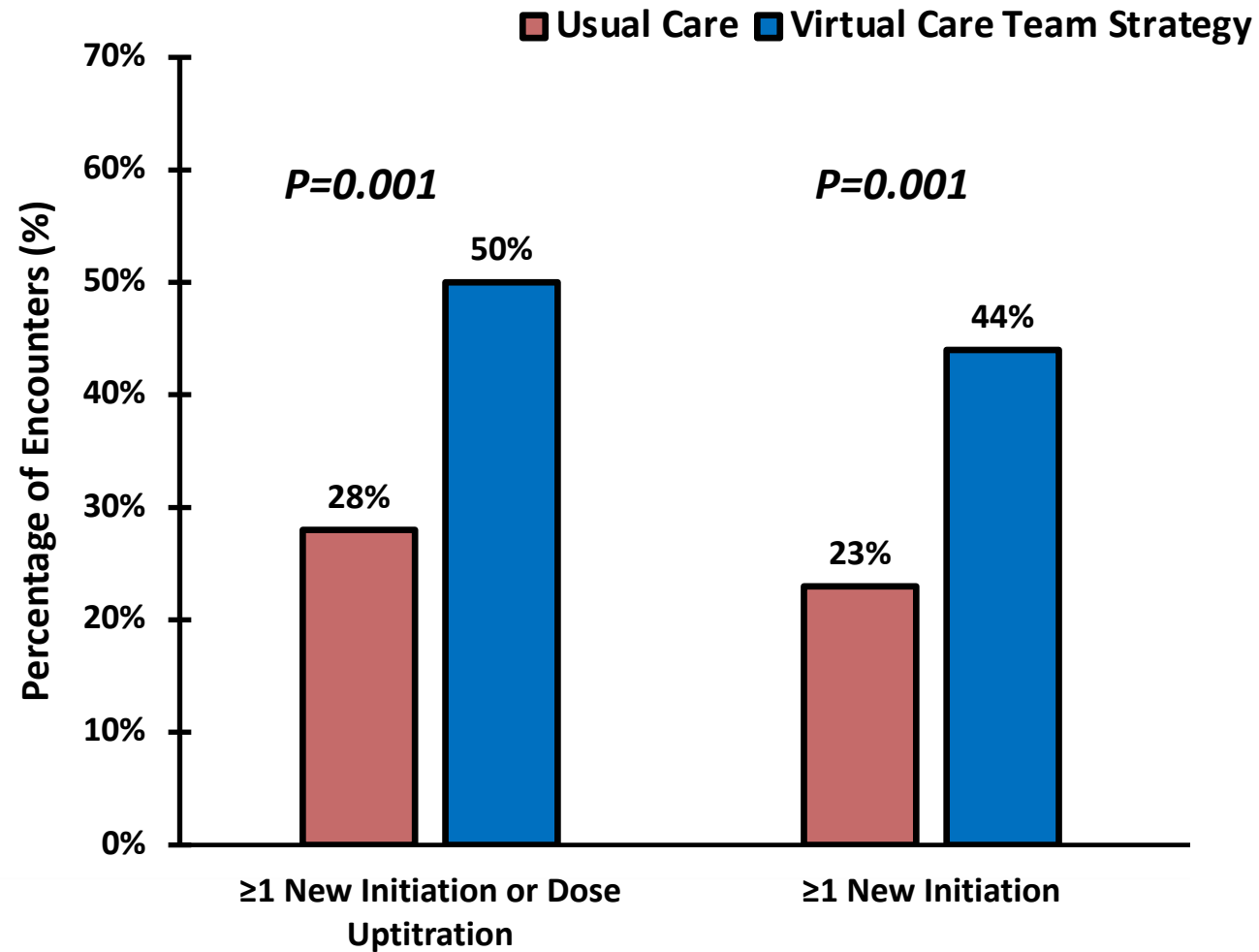
Secondary Outcomes



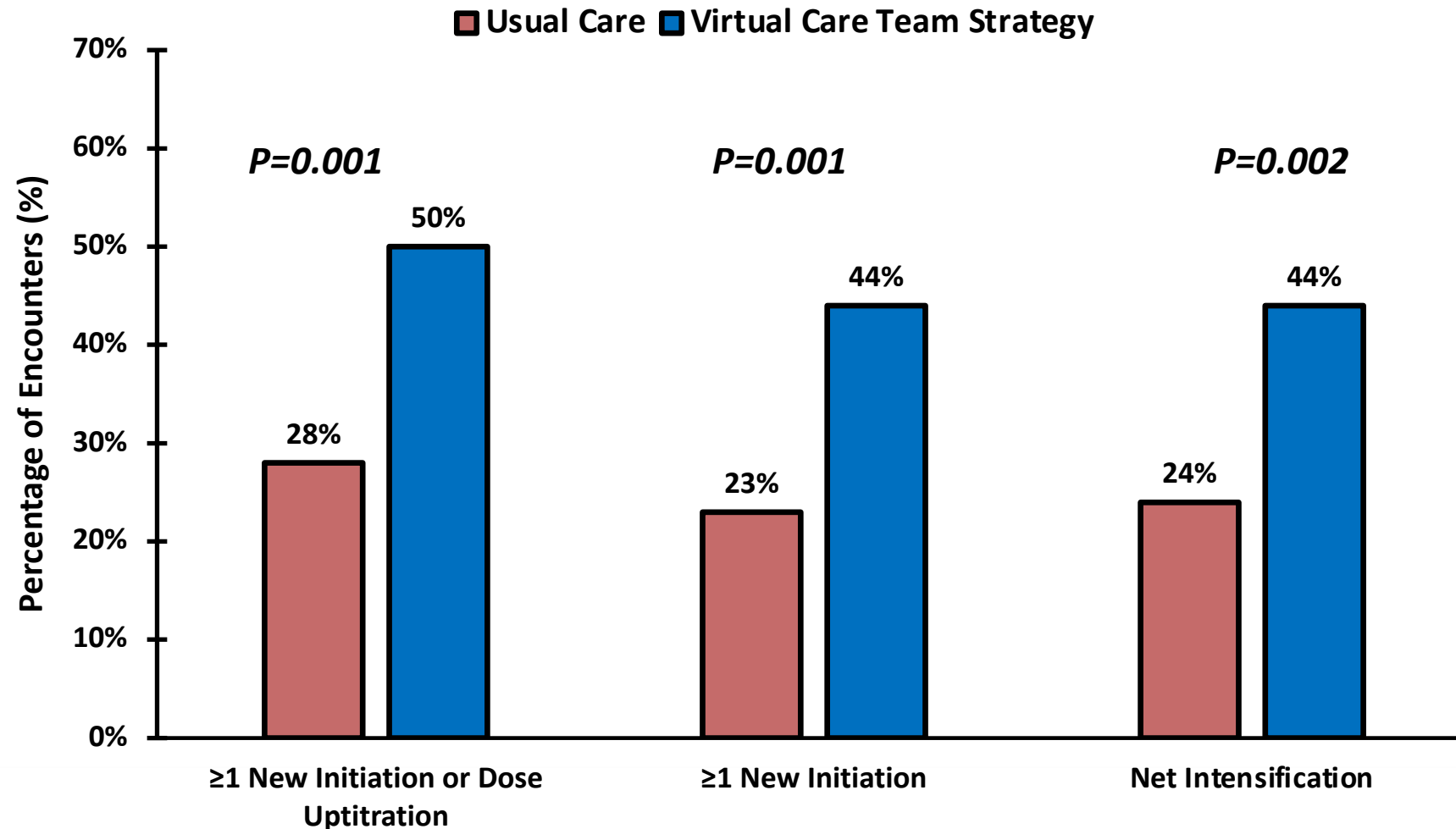
Secondary Outcomes



Secondary Outcomes

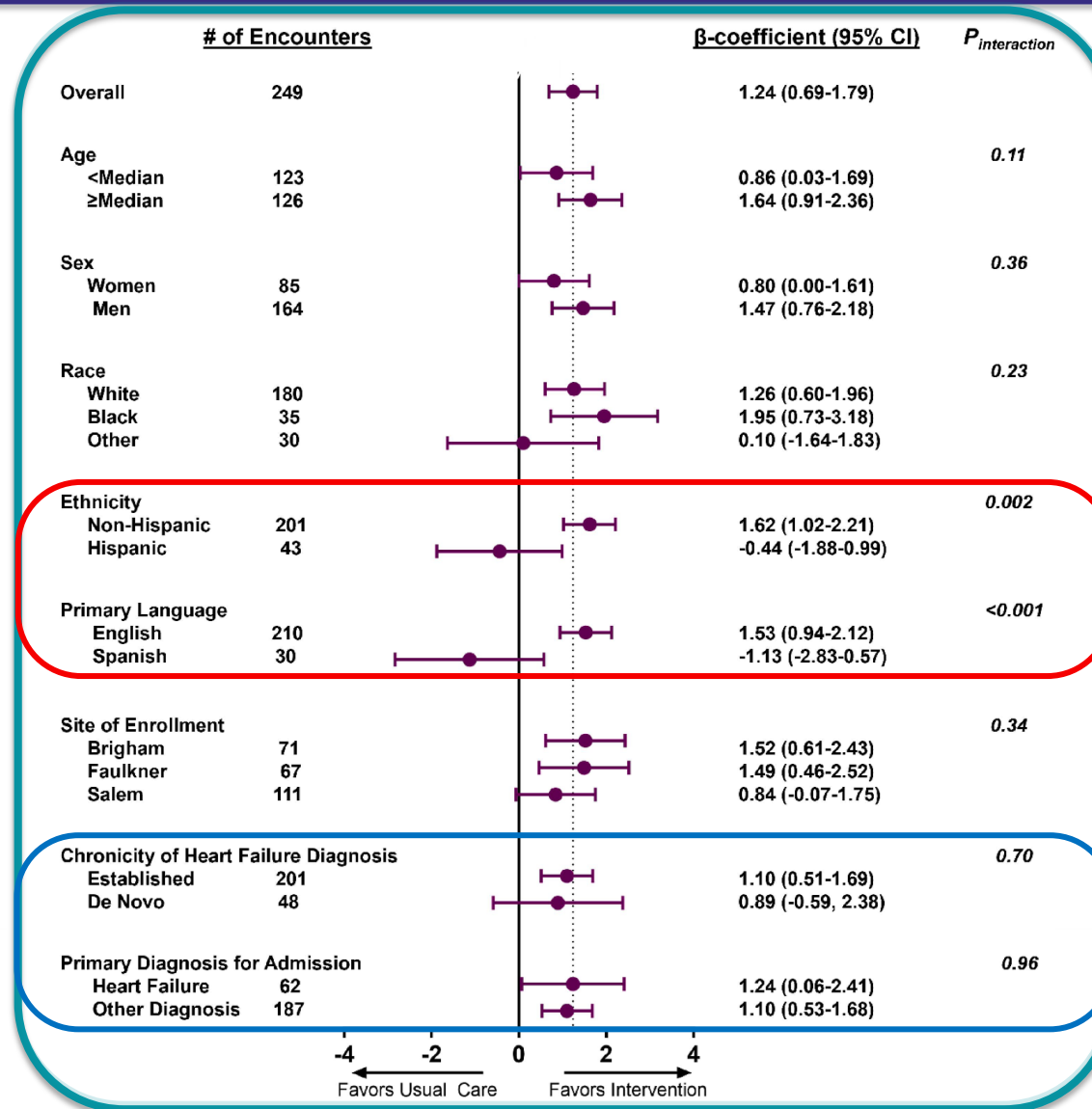


Secondary Outcomes



Number Needed to Intervene: ~5 Encounters

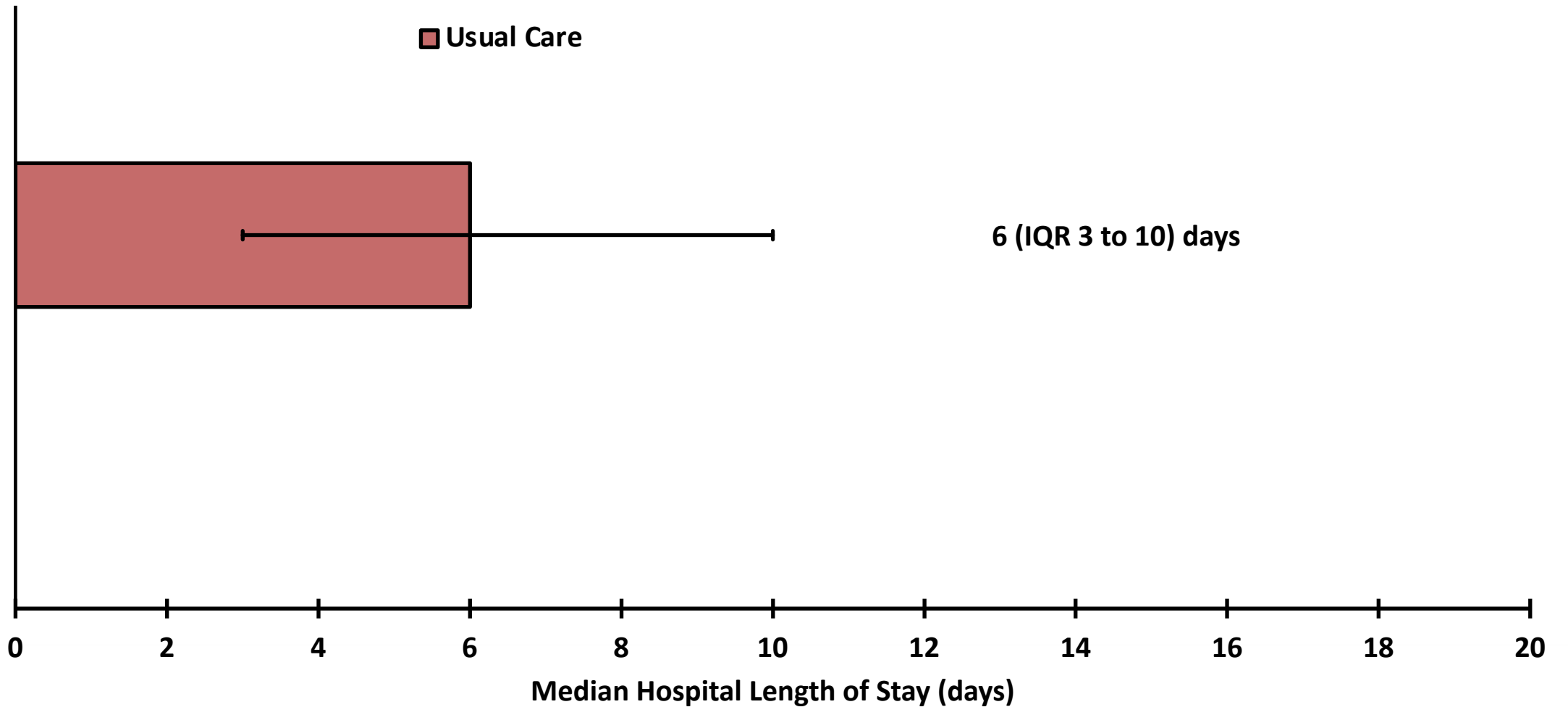
Primary Endpoint Across Subgroups of Interest



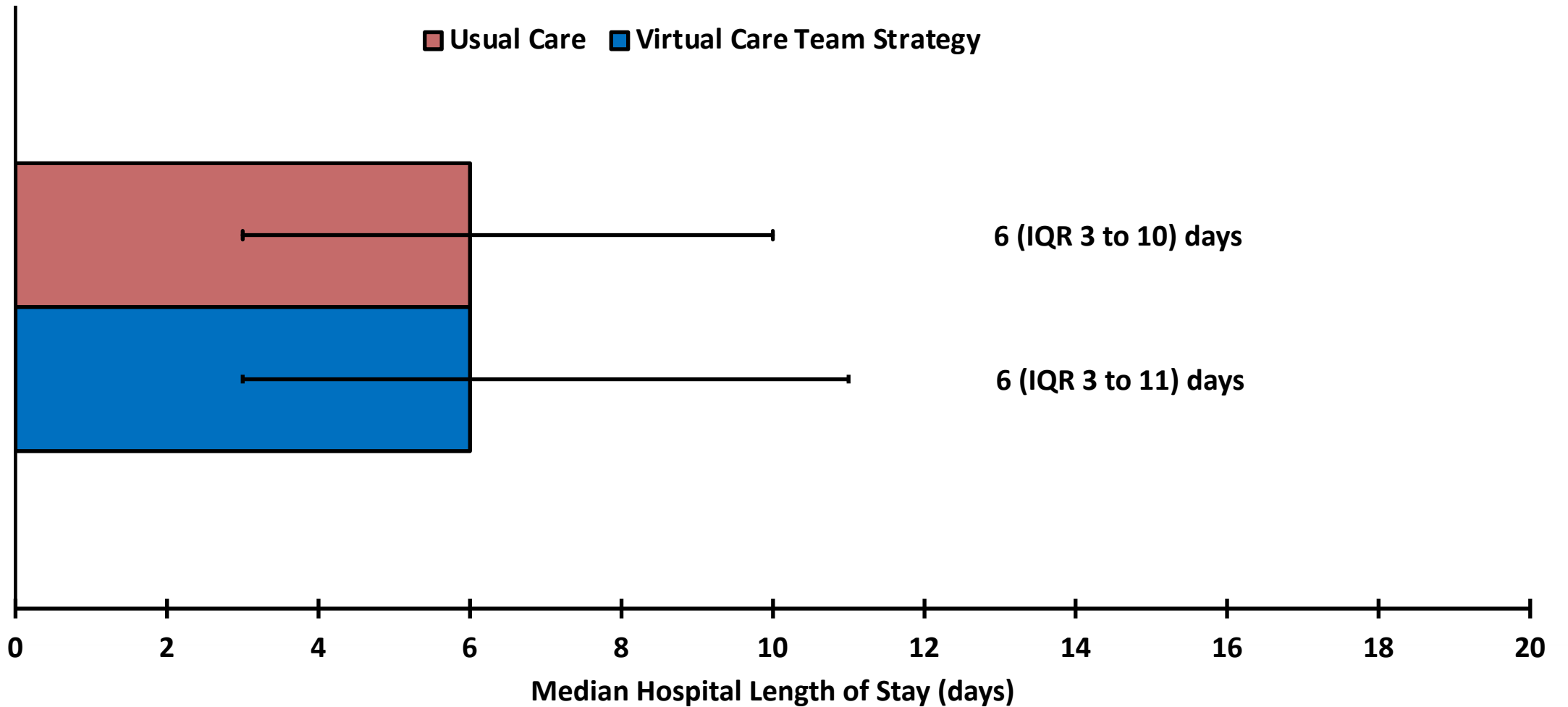
In-Hospital Adverse Events (CEC Adjudicated)

	Virtual Care Team Strategy n=107	Usual Care n=145	P-Value
Any Adverse Event	23 (21.5%)	40 (27.6%)	0.30
Hypotension	12 (11.2%)	24 (16.6%)	0.28
3 consecutive SBP <90mmHg	12 (11.2%)	23 (15.9%)	0.36
Vasopressor/ICU requirement for hypotension	2 (1.9 %)	7 (4.8 %)	0.31
Hyperkalemia	8 (7.5 %)	18 (12.4%)	0.22
Serum K⁺ > 5.5mmol/L	6 (5.6 %)	18 (12.4%)	0.08
Serum K⁺ > 6.0mmol/L	--	6 (4.1%)	0.04
Acute potassium lowering therapy	6 (5.6%)	6 (4.1%)	0.77
Acute kidney injury	5 (4.7%)	3 (2.1%)	0.29
Doubling of admission sCr	5 (4.7 %)	1 (0.7 %)	0.09
New kidney replacement therapy	--	2 (1.4 %)	0.51
Bradycardia	0 (0.0 %)	0 (0.0 %)	--
3 consecutive HR ≤40bpm	--	--	--
Temporary or permanent pacing	--	--	--
Acute heart rate therapy	--	--	--
In Hospital Death	1 (0.9 %)	2 (1.4 %)	--

Hospital Length of Stay



Hospital Length of Stay



Limitations

- The primary endpoint was an in-hospital implementation outcome; the impact of a virtual care team guided strategy on medication durability and clinical outcomes requires further study.
- Contamination of the intervention at the provider level is possible.
- The trial was conducted within diverse care entities a single healthcare delivery system; external validation is needed to establish generalizability.

Findings from the IMPLEMENT-HF Program

- A virtual care team-guided strategy improved medical therapy optimization in hospitalized HFrEF patients across multiple hospitals in an integrated healthcare system.
- Benefits were consistent across most subgroups, including hospitalizations for non-HF indications and *de-novo* HF presentations.
- We observed an important treatment interaction in which Hispanic & predominantly Spanish-speaking patients derived less benefit.
- A virtual care team guided strategy was safe, with no excess in adverse events.
- The beneficial effects did not come at the expense of increased hospital LOS.

Virtual care teams represent an effective, scalable, & safe approach to HFrEF therapeutic optimization.

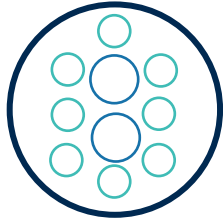


Virtual Care Team Guided Management of Patients With Heart Failure During Hospitalization

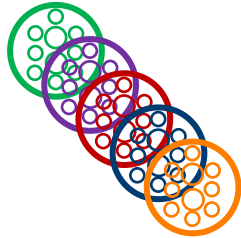


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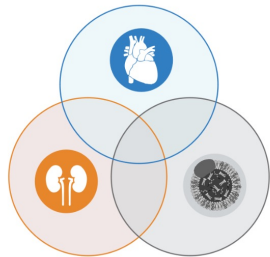
New Opportunities



Scaling Across a Health System



System-of-Systems Generalization

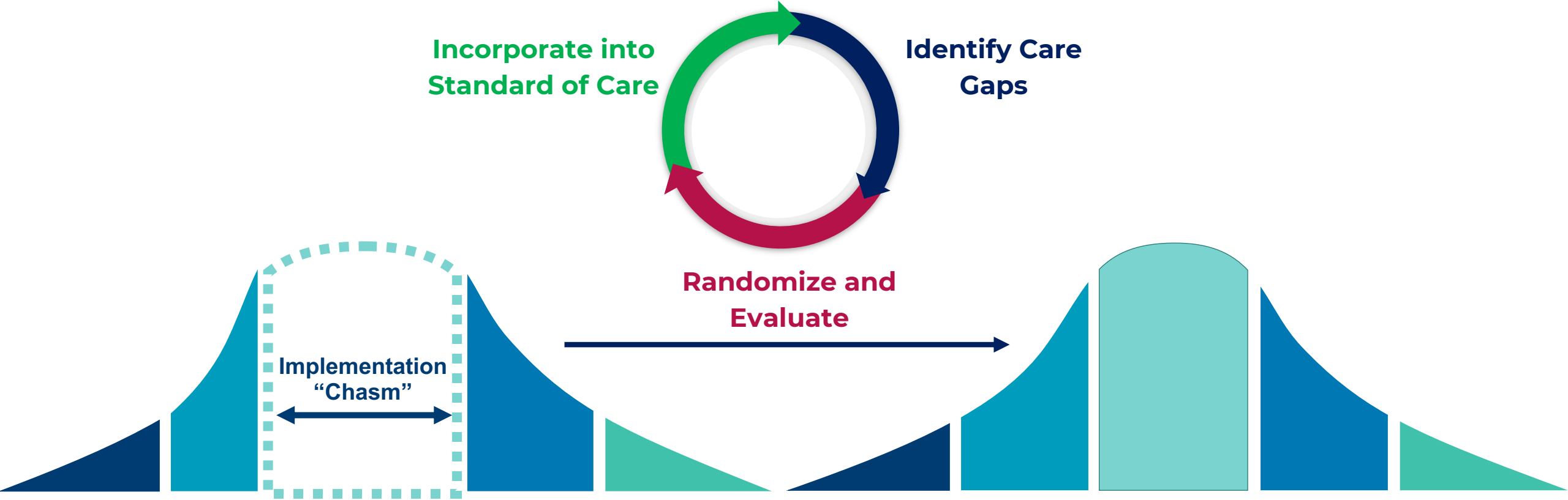


Cardiometabolic Care Implementation



Transitional Care

Learning to learn in a learning healthcare system



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Thank you

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